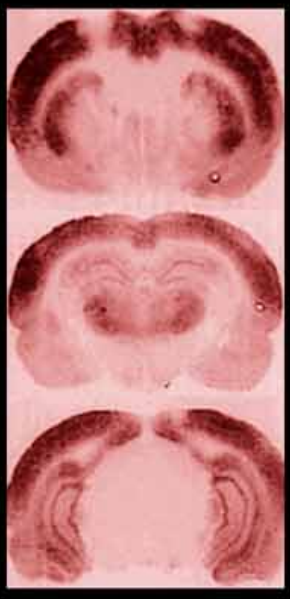
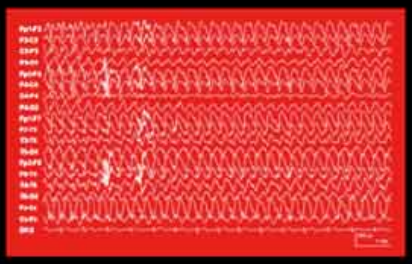
Status Epilepticus

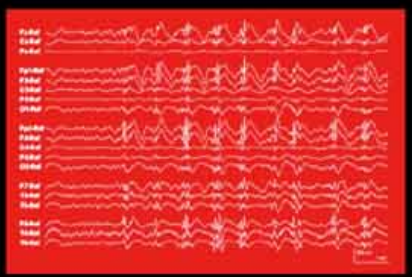
A Clinical Perspective

Edited by

Frank W. Drislane, MD







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Status Epilepticus

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A Clinical Perspective

Edited by

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HUMANA PRESS TOTOWA, NEW JERSEY

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Totowa, New Jersey 07512

www.humanapress.com

Production Editor: Nicole E. Furia

Cover design by Patricia F. Cleary

Cover illustration: Figures 4 and 8 from Chapter 5, "The Electroencephalogram in Status Epilepticus," by Susan T. Herman and Figure 4 C and D from Chapter 8, "Cellular Physiology of Status Epilepticus," by Omotola Hope and Hal Blumenfeld.

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Printed in the United States of America. 10 9 8 7 6 5 4 3 2 1

eISBN 1-59259-945-1

Library of Congress Cataloging-in-Publication Data

Status epilepticus : a clinical perspective / edited by Frank Drislane.
p. cm. -- (Current clinical neurology)
Includes bibliographical references and index.
ISBN 1-58829-355-6 (alk. paper)
1. Epilepsy. 2. Convulsions. I. Drislane, Frank. II. Series.
RC372.S767 2005
616.8'53--dc22

2004030486

Dedication

To my parents, Betty Kay and Edward Drislane, who gave me all I could want to start life, and to Rose, Catherine, Helen, and Edward, who help to sustain its enjoyment.

—Frank W. Drislane, MD

Series Editor's Introduction

There can be little doubt that status epilepticus is one of the most serious and challenging acute nervous system disorders to face the neurologic clinician. The mortality and morbidity of this disorder is high and the urgency of swift response is critical. Chapters describing its diagnosis and treatment have appeared in four previous volumes in the *Current Clinical Neurology* series including *Seizures: Medical Causes and Management* by Delanty, *Critical Care Neurology and Neurosurgery* by Suarez, *Handbook of Neurocritical Care* by Bhardwaj, Mirski, and Ulatowski, and *Seizures in Critical Care* by Varelas. The discussion of status epilepticus has now been greatly expanded in *Status Epilepticus: A Clinical Perspective* by Frank Drislane. The explosion of new information concerning the definition, classification, pathophysiology, epidemiology, electroencephalography, pathologic consequences, and treatment of "status" justifies this very impressive monograph on the subject. Given the urgency of prompt treatment of this potentially devastating disorder and the inherent difficulty of collecting reliable and useful clinical data, it is actually remarkable how much information has accumulated on the subject over the last several decades.

This is largely a clinical volume and a proper approach to the subject therefore begins with an all-inclusive classification. Whereas generalized convulsive and focal status epilepticus are familiar and have long been recognized, nonconvulsive status epilepticus is a more recent arrival on the scene that is all too often misdiagnosed and must first be appreciated in order to be properly recognized and treated. This very important topic is strongly emphasized in this volume with several chapters devoted to classification, differential diagnosis, descriptions of seizure "imitators," electroencephalographic patterns, clinical presentations, unusual behavioral and cognitive manifestations, and treatment as it specifically applies to nonconvulsive status epilepticus. Because "seizures beget seizures" the urgency of prompt diagnosis and treatment is obvious. This begins with the identification and management of underlying structural and metabolic causes and continues with the broad knowledge of the array of anticonvulsant treatments currently available for treatment of this disorder in all of its manifestations.

In recent years clinical neurology has evolved from a specialty emphasizing classical description and phenomenology to one that includes the management of the critically ill patient. There is no better example of this than the management of status epilepticus. In this volume, Dr. Drislane has brought together an impressive array of experts in the field that will serve to advance the state of the art of this critically important discipline.

Daniel Tarsy, *MD*

Preface

Status epilepticus is a wonderful field of study and of clinical activity. Its fantastically varied presentations offer insights into the workings of the human brain. Basic science and clinical studies of generalized convulsive status alone have taught us enormous amounts about brain processes, from cellular function to neuronal morphologic changes and cell death. The electrophysiology of status in both clinical and experimentally induced cases is instructive about neuronal connections and helps to explain brain function in pathologic conditions and in health. The many other forms of status epilepticus also illustrate brain mechanisms in widely varying ways.

Clinically, status epilepticus is worthy of intensive study. One of the primary values of the neurologist to his or her patients is the wise application of specialized knowledge and powers of observation in making accurate diagnoses of bizarre or baffling behavior that does not necessarily appear epileptic to others—or appears epileptic but is not. Focus on accurate diagnosis helps the neurologist to initiate appropriate and potentially beneficial treatment to combat serious illness.

The study of status epilepticus is undergoing exponential growth. It was recognized in antiquity, but only became the subject of medical writings in the late 19th century and of scientific laboratory studies just more than 30 years ago. The existence of nonconvulsive status was likely deduced by Charcot, but it only became clearly diagnosable after Berger developed the EEG in the mid 20th century.

It has been just a decade since the publication of Shorvon's monograph, *Status Epilepticus: Its Clinical Features and Treatment in Children and Adults*. Professor Shorvon lamented the fact that there were just 370 publications related to status in his review of a large database through 1978. Before his book, there was just the colloquium from Drs. Delgado-Escueta, Wasterlain, Treiman, and Porter (*Advances in Neurology Volume 34: Status Epilepticus: Mechanisms of Brain Damage and Treatment*) that served as a text for more than ten years. In the past decade, however, studies and writing on this subject have exploded, with hundreds of papers each year now. Consequently, over a thousand references are cited in this text.

Status Epilepticus: A Clinical Perspective attempts to bring together developments in the study of status epilepticus through 2004. It cannot cover all areas of investigation (especially the basic scientific) and stresses a clinical perspective. The book is organized along the lines of different forms of status epilepticus as encountered by the clinician "in the field." The underlying genetic, biological, and developmental background, as well as the precipitating factors that lead to an episode of status, are discussed within each of these areas. One sees a similarity but also a difference from one clinical form of status epilepticus to another, demonstrating that status is not a single disease, but rather arises from different substrates and comprises multifaceted illnesses.

Any understanding of status epilepticus requires its placement in a larger context, including its history, its differentiation from other neurologic and psychiatric illnesses, and its statistical delineation by epidemiologists. My gratitude goes to Drs. Kaplan, Dworetsky and Bromfield, and Waterhouse for their own perspectives tying the study of status epilepticus to the larger world.

Although *Status Epilepticus: A Clinical Perspective* focuses on the clinical presentations, diagnosis, and management of the many different forms of status epilepticus, all epileptologists are curious about its underlying biology. A better understanding of those topics is worthwhile for its own sake. We also hope and expect that treatment of status will be much better in a few decades; it will be the scientific discoveries in the field that make this come to pass. The chapter on cellular physiology and processes occurring during status epilepticus by Drs. Hope and Blumenfeld and that on the cellular damage and neuropathology of status by Dr. Fountain represent integral parts of the modern clinician's understanding of status, even when all of one's workday experience is in the clinical realm. References to pathophysiologic processes are also essential parts of other chapters.

Convulsive status epilepticus, that with uncontrolled and usually rhythmic and often violent movements, is recognized readily by most physicians and indeed probably by most citizens. The chapter on generalized status by Dr. Chang and that on the remarkably varied forms of focal status by Dr. Schomer show that this is a rich, complex field of study. These illnesses can be devastating, and even the treatment can be harmful, so a better understanding of their presentations and management is important for patients. If convulsive status (whether generalized or focal) has varied presentations, nonconvulsive status epilepticus might make the earlier categories appear relatively simple. Drs. Kaplan and Benatar show the extensive overlap of epilepsy and behavioral neurology in their chapters on the presentation of different forms of nonconvulsive status.

A book on status epilepticus without extensive reproductions and descriptions of EEG correlates would be nearly hemianopic. In her chapter, Dr. Herman offers a comprehensive view of the EEG and its use in status with striking illustrations that I believe seasoned electroencephalographers will find to be the classic examples one can keep in mind when reviewing less clear-cut or dramatic EEGs from patients who are in status epilepticus—or are thought to be in (or to have been in) status. Her chapter could serve as an atlas on the topic.

Treatment of status epilepticus is sometimes easier than diagnosis, but we and the patients are not always so fortunate. Happily, one of the major explosive areas of growth in publication and knowledge on status over the past decade has been on its management. Drs. Shih and Bazil review the treatment of generalized convulsive status epilepticus by the meticulous detailing of careful clinical studies. Traditions, myths and examples of dogma abound in this area. This chapter allows one to state what is actually known with any certainty. Fortunately (for the patients, if not for the up-to-date nature of this book) these studies will clearly have many companions soon. More will also be learned about the treatment of refractory status epilepticus, but at this point, the chapter by Drs. Smith and Bleck is as current as

possible and from authors with as much experience as an editor can find. Studies on the treatment of nonconvulsive status have been far less rigorous, but I have attempted to summarize them.

Status epilepticus in very young children and neonates often appears to those of us in adult neurology to be a totally separate and mysterious illness. Drs. Riviello and Gaitanis bring a coherent perspective to the field while describing tremendously different syndromes and problems. Their review of the varied presentations and their extensive clinical experience should serve as useful guides to evaluation of children with status; treatment is discussed in detail. Differences from adult neurology in approach to children and neonates are emphasized.

There are obvious areas of this book to which some readers could fairly object—including overlapping material among the chapters and the lack of a completely consistent dogma in both diagnosis and treatment. The overlap is hard to escape when individual clinical problems are difficult to fit into occasionally arbitrary categories. I hope and believe that the overlap is acceptable, particularly noting that each author has slightly different perspectives on the same questions, and those different perspectives can enrich one's appreciation for the large world of status epilepticus.

Similarly, with the many authors' clinical expertise, it can be helpful to see the same problem or question addressed from different viewpoints and with somewhat different approaches. I suspect that nearly every author would tackle an individual patient's clinical problem in a very similar way, but often there is no one right answer and nothing unusual about finding partially conflicting recommendations for an individual situation. In 2004, there are still debates about definitions, diagnoses, and treatments of different forms of status epilepticus. Controversy and speculation were not proscribed, but rather encouraged. Different opinions persist and are reasonable. The authors have varied insights and styles. These multiple approaches constitute not so much inconsistency, as different perspectives based on rich experience, and it is hoped that those variations will be educational and possibly even stimulate new and better studies.

What I believe to be the high quality of the syndrome descriptions, clinical insights, and guidance on treatment is owed to my colleagues and coauthors. This is largely a group of academic neurologists and epileptologists from the Northeastern United States (which includes Virginia if one looks topographically rather than historically). Much wonderful work on status epilepticus comes from California, other parts of the United States, Britain, France, and many other lands around the world. This is a field that has evoked, by its intrinsic interest and clinical urgency, a productive collegial international cooperation that is both enjoyable and beneficial. The work of others is referred to extensively, but the authors were solicited from personal contacts through the world of neurology and epilepsy and chosen for their academic achievements and because I knew that they could not fail to write outstanding, clinically oriented chapters based on both careful study of the literature and rich personal clinical experience. I have enjoyed learning from their writings—and am confidant that I will not be the last to do so.

It is a pleasure to thank Ms. Nicole Furia and her colleagues at Humana Press for their patience and encouragement and the invitation to organize and write this book. All the authors are clearly indebted to our patients, residents, and colleagues who share and collaborate in our clinical experience that has led to our learning about status epilepticus. They have helped to clarify our thinking. We hope that *Status Epilepticus: A Clinical Perspective* will help kindle an interest in status epilepticus in our younger colleagues and an interest in investigating it further. We believe that a better understanding of basic and clinical science is not only enjoyable, but will also help the many patients who will have status epilepticus in the future.

Frank W. Drislane, *MD*

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I General Topics

1
History of Status Epilepticus

Peter W. Kaplan

Although seizures have been described since ancient times, it is surprising how scant are the descriptions of what today is clearly identified as status epilepticus (SE). Perhaps the earliest reference to the condition of epilepsy and prolonged, ongoing seizure activity—SE—may be found in the Sakikku Cuneiform Tablet *(1)* (Fig. 1), which notes:

> If the possessing demon possesses him many times during the middle watch of the night, and at the time of his possession his hands and feet are cold, he is much darkened, keeps opening and shutting his mouth, is brown and yellow as to the eye. It may go on for some time, but he will die. (XXV–XXVI Tablet Obverse 718–612 BC)

Caelius Aurelianus *(2)* notes that "fits can recur . . . even in the same day," and comments further on the mortality when "the attack extends into the second day." Saul, while prophesying at Ramah, was to be diagnosed as having status epilepticus *(3)*.

During the renaissance period, Thomas Willis *(4)* in England noted:

> [W]hen as fits are often repeated, and every time grow more cruel, the animal function is quickly debilitated; and from thence, but the taint, by degrees brought on the spirits, and the Nerves serving the Praecordia, the vital function is by little and little enervated, till at length, the whole body languishing, and the pulse loosened, and at length ceasing, at last the vital flame is extinguished.

All in all, however, descriptions of status epilepticus are few throughout most of antiquity with only an occasional note on status epilepticus in the late 18th and early 19th centuries. Descriptions have been provided by Lysons, Heberden, and Good, as cited by Hunter *(5),* but it was in France that the expression *état de mal* was used in Paris at the Salpêtrière and Bicêtre hospitals for some time before it would be found in written form in the University Dissertation of Calmeil *(6,7)*. Temkin quotes from Delasiauve (Traité de l'épilepsie) that *"À la Salpêtrière . . . on les désigne vulgairement sous le nom d'état de mal"* ("At the Salpêtrière we commonly referred to them as an *état de mal"*), while Trousseau notes, *"Vous avez cependant entendu parler de faits dans lesquels des attaques ont duré deux, trois jours, et se sont terminées par la mort. C'est là ce qu'on a appelé, à la Salpêtrière et à Bicêtre, l'état de mal."* ("You, however, have heard of circumstances where fits have lasted two or three days,

From: *Current Clinical Neurology: Status Epilepticus: A Clinical Perspective*
Edited by: F. W. Drislane © Humana Press Inc., Totowa, NJ

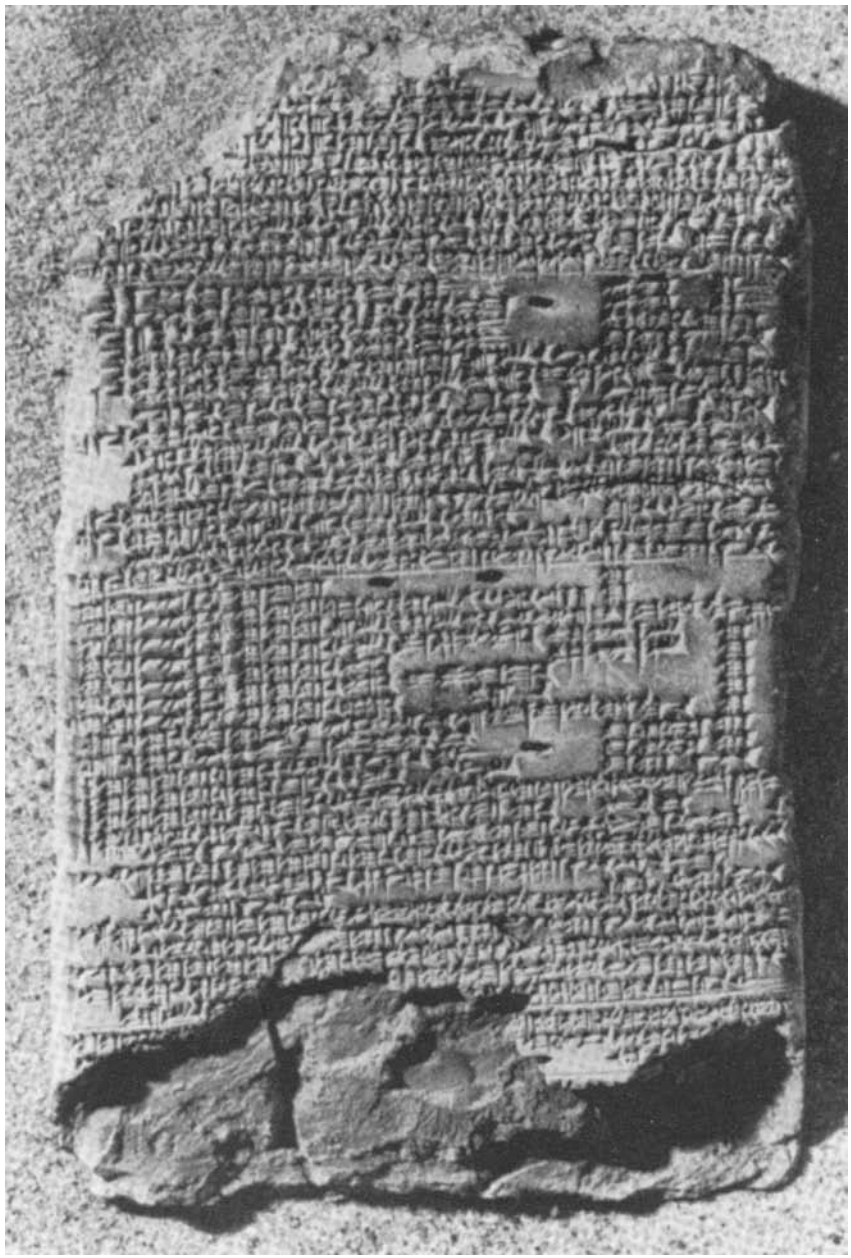

Fig. 1. Epilepsy tablet in the British Museum. (Reprinted with the permission of the British museum.)

and ended in death. It is in these cases that one spoke, at the Salpêtrière and at Bicêtre, of *état de mal* [status epilepticus].") According to Calmeil, this term goes back to the patients' use of the term: *"C'est ce que les maladies appellent entre eux état de mal."* ("It's what the patients among themselves called status epilepticus.") Calmeil differentiated between the severity of fits and SE, describing a series of epileptic seizures that followed without interruption, and indicated a poor prognosis *(6,7)*.

The use in English of *status epilepticus,* however, finally appeared when Bazire translated Trousseau's lectures on clinical medicine *(8–10)*. As Shorvon notes, the condition of status epilepticus was barely recognized when Calmeil defined the term, and it had not been separated from epilepsy as a whole *(8)*. Previously, it had been assumed that SE was a separate entity rather than a condition of repeated seizures. It was now seen to represent the "maximum expression of epilepsy," *(8)* with its own particular characteristics, albeit confined to tonic-clonic seizures. Temkin's footnote on Hunter states that, "Hunter has shown that reports of this condition were very rare before epilepsy was studied in hospitals and remained rare until the introduction of potassium of bromide into the therapy of epilepsy" *(7)*.

In Britain, cases of status epilepticus were described by Gowers, Ferrier, Jackson, Horsley, Turner, Sieveking, and Coleman *(8)*. The study of epilepsy flourished in Paris at the Salpêtrière, which, with 8000 patients, was Europe's largest asylum. Physicians practicing at the Salpêtrière and Bicêtre (including Calmeil, Pinel, Esquirol, and Charcot, as well as Bourneville and Trousseau, working at Hôtel Dieu), provided extensive clinical descriptions of status epilepticus, with Charcot's pupil, Bourneville, defining SE as a "serious complication" of epilepsy that could be seen to occur in five stages. As summarized by Shorvon, they are: (1) the repetition, more or less incessant, of seizures that in consequence often become subintrant; (2) *collapsus*, which varied in degree of severity from transitory loss of consciousness to complete and irreversible coma; (3) hemiplegia, more or less complete, but transitory; (4) characteristic rates of pulse and respirations; and (5) marked rise in temperature, persisting in intervals between seizures and intensifying after the seizures ceased *(8)*.

Trousseau, working at Hôtel Dieu, also provided some of the early descriptions of status epilepticus, distinguishing isolated seizures from those "which are repeated in rapid succession and end in the death of the patient." He also noted that petit mal seizures might appear with sufficient repetition, "that one seizure would become confused with the next, simulating a continuous seizure which might persist for two or three days" anticipating the demonstration of absence status. Since both petit mal and grand mal seizures were seen to occur in the same individual, he believed this pattern to be part of a seizure tendency, an approach that was also taken when syndromes were applied *(8)*.

Writing in 1903, Clark and Prout described the pathological and clinical appearances of status epilepticus in 38 patients *(11)*. These cases provided examples of the maximum development of epilepsy described as a fusion of successive convulsions to the point of coma and exhaustion, eventually associated with increases in pulse, respiration, and temperature. Clark and Prout noted durations ranging from 2 to 9 d,

associated with changes in reflexes, pupil responses, and lateral and upward eye movement, eventually leading to clamminess of the skin, bodily wasting, and bedsores. The last phases were marked by respiratory exhaustion, often resulting in death *(11)*.

Even as the apparently striking features of convulsive status epilepticus were overlooked until relatively recent times, the concept of demonic or divine possession of the patient who displayed "seizures," but without convulsions, had long preoccupied medieval medical and public minds. Asylums later built in France and the United Kingdom became repositories for such patients, along with patients with more obvious convulsions. With the increasing recognition and understanding of diseases of the mind, hospitals in the 1800s, particularly in France, would often also serve as lunatic asylums *(12)*. The term *furor epilepticus* was used to refer to episodes of madness, frequently with violence. "Epileptic delirium," "epileptic mania," and "*fureur épileptique*" connoted conditions present after ictal coma. One such description at the time was *(12)*:

> [T]he face is flushed, and the aspect of the patient is like that of a man under intoxication: he attempts to start from bed and run about, and on being withheld, vociferates and endeavors to overcome resistance. It continues commonly one, two, or three days, during which the patient requires confinement in a strait jacket, and then gradually subsides, and the patient returns to his previous state.

Other allied states of epileptic confusion or wandering were described. Epileptic ecstasy or epileptic somnambulism was described by Prichard *(12)*:

> A more unusual circumstance in the history of epilepsy is the appearance of a species of somnambulism, or a kind of ecstasis during which the patient is in an undisturbed reverie, and walks about, fancying himself occupied in some of his customary amusements or avocations.

Sir Samuel Wilks *(13),* who used bromides in treating epilepsy, described a patient who was:

> in the condition which is popularly called 'lost'; he is scarcely conscious of acts and conversation going on around him, yet he may continue walking in a given direction, showing that his movements must still, in a measure, be guided by his senses. He is in a dreamland, and is indeed in much the same state as a somnambulist. This condition under many varieties of form is called the status epilepticus, although the term is more usually applied to the case where the patient lies for a lengthened period in a kind of trance or stupor, as, for example, in the case of a man lately in the hospital, who after a succession of fits, lay for hours in a state of lethargy. In the milder forms it is one of great interest from a physiology point-of-view and seems to point to the possibility of a subconscious state, in which the brain is sufficiently active to control the spinal system and yet not awake enough to excite the feeling of consciousness. In reference to the influence of the brain on the muscles and necessity of consciousness to preserve their tone, the condition is one full of interest.

The nonconvulsive states of automatism received the attention of Jules Falret (1824–1902) who referred to them as "*petit mal intellectuel*" *(14)*. "Such a patient might leave home or work, with clouded mind, dull in thought, subject to unprovoked anger and

fits of despair, . . . he was forgetful, had complete lapses of memory, headaches and 'étourdisement' [giddiness], noted luminous sparks, frightening objects and visions" *(14)*.

Höring *(15)*, in Germany, described a patient who:

> suddenly falls into a state of deep dreaming and stretches his hands in front of him. These together with his head and the upper part of his trunk begin to tremble. At other times he runs away during the attack and talks gibberish or he searches, as in a dream, in all of his pockets as if he were missing something, or he makes scrubbing or rubbing motions on his trousers; sometimes he answers if addressed during this dream state, but usually wrongly, and at its end he usually closes his eyes, seems to sleep for a few minutes, and then has no idea what happened.

In the late 1800s Charcot, in Paris, believed that somnambulistic states derived from ongoing ictal conditions; to press his point, he presented a patient in his "*Leçons du mardi"* at the Saltpêtrière Hospital in Paris *(16)* (Fig. 2). This 37-yr-old Parisian delivery man wandered about Paris and even to the coast, at Brest, being arrested on one occasion, and released only on the cognizance of Charcot. Charcot treated the patient with bromides, but in an early example of noncompliance (possibly because of impotence frequently attributed to bromide therapy) the patient began his wandering again *(16)*. In Britain, Gowers *(17)* speculated that similar states, rather than being ictal, occurred after the seizure:

> After epileptic fits of moderate severity, the patient may pass into a condition of mental automatism, in which various acts are performed in an apparently conscious manner, but of which no recollection is afterwards retained.

Gowers, in his work *Epilepsy (18),* refers to the studies of Bourneville and provides one clinical description, noting that:

> "the intervals between the fits becomes shorter, the coma deepens, the pulse and respiration become very frequent, and the temperature rises, it may be of 104°, 105°, or even 107°. Sometimes hemiplegia comes on after the condition has existed for several days. The patient may die in a state of collapse, death being apparently due to the voilent and almost continuous convulsions, or, the fits ceasing, he may become delirious and present symptoms of meningitis, with rapid formation of bedsores, and may die in this stage. At any period, the symptoms may lassen, and the patient recover. A large proportion of the cases, however, end fatally. Fortunately, this severe degree of the status epilepticus is very rare, at any rate out of asylums for the insane. No instance in which death occurred has come under my own observation, although I have seen many examples of a slighter degree of the condition, from which the patient have recovered." (*18*; pp. 193–194)

While addressing treatment, Gowers *(19)* offers little reassurance:

> "in the 'status epilepticus,' in which attacks recur with great frequency for several days, and in which bromide often fails entirely, I have known hypodermic injections of morphia, in doses of 1/16th of a grain to be of great service, and Sieveking has found it useful, given by the mouth, in the same state. But morphia is a remedy which can only be employed hypodermically in epileptics with extreme caution. If an attack occurs, and the post-epileptic coma coincides with the sleep induced by morphia, the patient's life is in great danger." (*19*; 273)

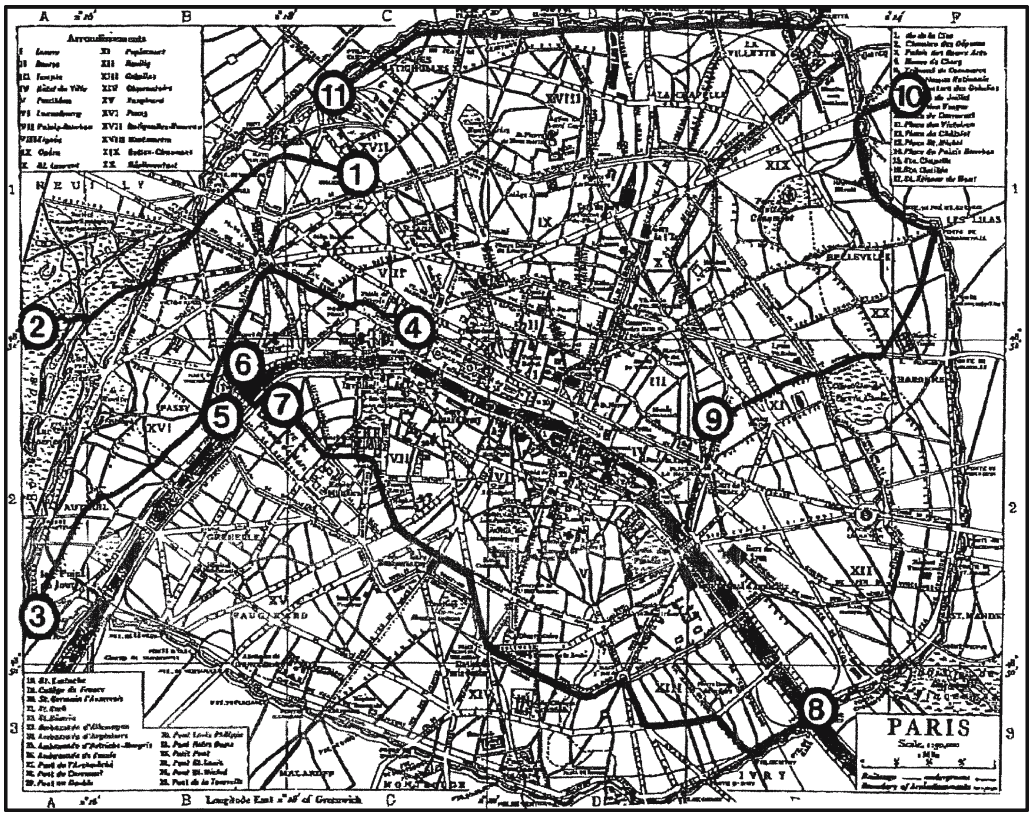

Fig. 2. Map of Paris in the 1880s showing the peregrinations taken by a mailman with bromide-responsive epileptic "wanderings"—an early case of nonconvulsive status epilepticus? (From ref. *8*; reprinted with the permission of Cambridge University Press.)

He goes on to note:

> In the status epilepticus, bromide often fails. Inhalations of nitrite of amyl have been found useful by Crichton Browne. Chloroform inhalations rarely have a permanent effect. The remedies from which I have seen most good are repeated dosages of chloral, the subcutaneous injection of morphia, and the application of ice to the spine. (*19*; pp. 290–291)

Thus long neglected in the written records of medicine, it would seem that status epilepticus has been addressed within the greater context of epilepsy only over the past few hundred years. Careful observations of individual cases in association with gross anatomical and classic histological correlation led to its identification as the "maximum expression of epilepsy" *(8)*. After 1924, when Berger discovered the recordable electrical impulses from the brain by electroencephalography (EEG), there was initially a concerted effort to link the now-measurable brain dysfunction with its clinical correlates.

The modern era of recognition and analysis of SE perhaps begins with the Marseille colloquia of 1962 and 1964, where classification and definitions for seizures and status epilepticus were promulgated *(20)*. Since the 1960s, greater attention has turned to the physiologic underpinnings, neurochemistry, and pharmacology of status epilepticus, most recently with functional imaging techniques.

As with convulsive status epilepticus, it was the advent of EEG that proved, beyond doubt, that nonconvulsive status epilepticus derived from an epileptic brain, and not, as some had suspected, from hysterical or nonepileptic fugue states. Lennox used the EEG to diagnose absence status epilepticus in 1945 *(21),* followed in 1956 by Gastaut and Roger, who described a nurse with complex partial status epilepticus (CPSE) that had lasted, possibly, several months *(22)*. The stage was now set for modern electroclinical correlation with video-EEG monitoring and more profound investigation of SE using functional imaging.

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2

Types of Status Epilepticus

Definitions and Classification

Frank W. Drislane

What is status epilepticus? For all the criticisms leveled at the now-traditional definition accepted by the International League Against Epilepsy (ILAE) and based on the 1962 Marseilles conference, "a condition characterized by an epileptic seizure which is so frequently repeated or so prolonged as to create a fixed and lasting epileptic condition" *(1),* this definition *does* capture the concepts nearly everyone wants. The condition is necessarily epileptic, i.e., related to abnormal electrical activity in the brain with a clinical, and unhealthy, alteration in neurologic function. The patient in status epilepticus (SE) is clearly in a different and worse state than one who has an individual epileptic seizure only. Shorvon notes that SE is "not simply an iterative version of ordinary epilepsy" *(2)*. Whether it is a more serious and fulminant etiology of seizures that produces their prolongation and repetition, or whether there is a fundamentally different failure of inhibition (more than occurs between a spike and a clinical seizure), the patient in status epilepticus has entered a new and worse condition. Discrete epileptic seizures come to an end, although there may be a prolonged postictal state. In SE, however, there is a definite clinical imperative to interrupt seizures because the patient may suffer grievous harm otherwise. Not only are there extensive physiologic, and sometimes pathologic, changes occurring during SE *(3)*, but there is also a fundamentally different and urgent clinical problem for the patient and physician.

1. NATURE AND DIAGNOSIS OF STATUS EPILEPTICUS: WHAT ACTIVITY CONSTITUTES STATUS?

Extensive controversy persists over what type of clinical or electroencephalograpic (EEG) activity constitutes status epilepticus. There are four primary components to the diagnosis: clinical manifestations (i.e., symptoms and signs), the duration of these events, EEG manifestations, and a response to anticonvulsant medication. Different components and criteria are more important, depending on the purpose of the definition, e.g., whether one is deciding to initiate treatment (in which case, clinical manifestations are primary, and a rather short duration should be

From: *Current Clinical Neurology: Status Epilepticus: A Clinical Perspective*
Edited by: F. W. Drislane © Humana Press Inc., Totowa, NJ

sufficient) or selecting cases for a clinical research review—in which case one might apply all the criteria, in what may be considered the neurologic equivalent of a medical diagnosis confirmed with tissue pathology.

1.1. Clinical Manifestations: Symptoms and Signs

Clinical manifestations of status epilepticus are primary. They are often sufficient and persuasive for diagnosis, such as with clinical motor activity, including ongoing rhythmic jerking activity or more dramatic tonic and clonic movements or intermittent generalized convulsions. Whatever the EEG findings or response to medication (or lack of either), all will accept these signs of ongoing epileptic seizures as diagnostic of SE. Those with motor manifestations, including automatisms or major alterations in behavior, are easier to diagnose. Nonconvulsive SE may be suggested clinically but often requires EEG to help make the diagnosis. The many different clinical forms of status epilepticus, their different definitions, methods of diagnostic determination, the many different clinical manifestations and consequences, and appropriate treatments, are the subjects of many chapters in this book.

1.2. Clinical Manifestations: Duration

Much dissatisfaction with the "fixed and lasting" definition results from its not specifying an exact time requirement. It often goes unacknowledged, however, that a precise temporal definition requires specification of the type of status epilepticus being timed. Most of the data brought to bear on such discussions involve generalized convulsive status epilepticus (GCSE); other types of SE are often not mentioned. The classic definition of SE captures the essence of the problem, but different durations should apply to different types of SE, i.e., whether one is refering to GCSE, focal motor status, or nonconvulsive status epilepticus (NCSE), and so on. Using a single duration as part of the definition for all forms of SE is no more possible or desirable than devising a single definition of "heart disease."

For decades, clinicians faced with the temporal imprecision of the ILAE definition have imposed a 30-min criterion *(4)*—without international agreement or clear clinical or experimental support. This may represent a reasonable compromise between the time provoking neuropathologic consequences of SE in experimental animals on the one hand and clinical urgency in humans on the other.

Lothman and others have detailed the physiologic deterioration that occurs in human GCSE, often after about 30 min *(3)*. Pathologic concomitants are speculated upon as occurring in parallel. While no experimental paradigm for SE in animals can capture all the features (from cellular to clinical) of human SE, the work of Meldrum and colleagues 30 yr ago provided a superb experimental model, at least for GCSE *(5–7)*. In those experiments, baboons had SE induced by administration of bicuculline, and ensuing seizures included convulsions and prolonged, rapid epileptiform discharges, typically lasting hours. Even with the systemic factors of acidosis, hyperglycemia, and hypoxia prevented by paralysis and ventilation, animals with rapid, prolonged epileptiform discharges incurred neuronal damage and loss in the hippocampus and elsewhere. Most of these animals had SE for far longer

than 30 min. At some later point, damage appeared to accrue. Nevertheless, the *clinical* choice of 30 min was reasonable, especially in keeping with the physiologic deterioration *(3)*. The timing with respect to pathologic changes is less certain, but a 30-min criterion shows prudent concern for the threshold of damage in humans.

For actual patients, however, there is clearly no reason to observe without intervening after frequent or continuous seizures short of 30 min. That criterion is often used retrospectively in describing patients with prolonged seizures or SE, but no reasonable physician would withhold treatment for 30 min. Accordingly, no *prospective* study of the treatment of SE can use the 30-min criterion derived from experimental (i.e., nonhuman animal) models.

Because of the clinical urgency in treating SE, durations required for diagnosis have been plummeting over the past few decades. The largest trial of different antiepileptic drugs (AEDs) for the treatment of GCSE covered 518 patients with clinical GCSE or "subtle" SE determined by EEG *(8)*. In that trial, it was considered mandatory to begin treatment within 10 min—still retaining the label of SE. Patients with less obvious or "subtle" SE and those not responding to the initial treatment were particularly refractory and had a high mortality.

Subsequently, in a prospective, randomized trial covering 205 patients with repetitive or prolonged generalized seizures treated by San Francisco emergency medical technicians (EMTs) with diazepam, lorazepam, or placebo, "prolonged seizure" was defined as 5 min, and treatment was begun as soon as possible after that *(9)*. The intent was to interrupt SE, but not to wait for 30 min to establish a traditional diagnosis. Beneficial effects were found for benzodiazepine treatments begun before emergency room arrival.

These clinical studies were randomized, prospective studies with human subjects. There was a clinical and ethical imperative to treat quickly. Such trials must define SE as diagnosable within several minutes. Consequently, there is a large difference in duration between the SE that led to neuronal damage experimentally and the shorter duration of SE now felt to warrant urgent treatment. Accordingly, Lowenstein, Bleck, and Macdonald proposed an "operational" definition of GCSE, i.e., 5 min, the time by which SE should be interrupted to avoid morbidity, mortality, or refractory SE *(10)*.

An "operational" definition of status epilepticus is appropriate to guide clinical activity. In a National Institutes of Health (NIH) study of 120 secondarily generalized tonic-clonic seizures in 47 patients evaluated for refractory epilepsy, Theodore and colleagues found that the mean duration of a generalized convulsion (as reviewed on videotape) was 62 s; only one lasted longer than 2 min *(11)*. They concluded that a duration of 2 min was outside the normal range for a discrete, individual seizure and that intravenous AEDs should be administered at that point. Certainly, seizures proceeding for at least 10 min appear much less likely to stop spontaneously *(12,13)*. Some may do so, but the physician cannot rely on that in an individual patient. The situation calls for treatment, just as with conventionally defined status epilepticus.

Studies cited so far refer to GCSE, but there are necessarily several different, simultaneous, and reasonable definitions of status epilepticus for *different types* of SE. Definitions differ depending on whether one is diagnosing an individual patient in a clinical setting or reviewing a group's experience with patients with an ironclad diagnosis appropriate for clinical research. For GCSE in *retrospective* studies, *30* min should probably remain the standard definition, at least if it is desired to compare results from one study to another. As the "operational" and other shorter duration definitions become more readily applied clinically (as well they should be), it is very likely that outcomes will appear to improve. For example, in the study of DeLorenzo and colleagues, patients with shorter durations of ongoing, continuous, or repeated seizures without recovery, lasting 10 to 29 min (not quite long enough to warrant a classical diagnosis of SE), had a significant mortality but less than that for patients with SE diagnosed after 30 min *(12)*. Presumably, patients treated after 5 to 10 min will do better than those treated after 30 min. This does not mean that short duration definitions are inappropriate or lead to inferior studies. Rather, definitions need to be stated clearly before reporting the outcome of any group of patients labeled as having status epilepticus.

1.3. EEG Manifestations

Often, the diagnosis of GCSE is made readily by clinical observation, but some forms of SE require EEG to help make the diagnosis. At the extreme of subtle or completely inevident clinical manifestations, the diagnosis may depend almost entirely on EEG. If clinical and "duration" components of SE definitions are controversial, they provide an island of relative tranquility in the stormy sea of debate over EEG criteria.

1.3.1. Discrete Seizures vs Continuous Discharges

More than 30 min of recurrent, discrete electrographic seizures on the EEG will satisfy almost all epileptologists as evidence of ongoing SE. In this case, the EEG is persuasive, even without any clinical manifestations during the intermittent electrographic seizures. The diagnosis holds even when the outcome can be attributed to the underlying disease rather than to recurrent seizures. Such discrete electrographic seizures occurred in 8 of 26 patients with depressed consciousness after subarachnoid hemorrhage (but without clinical seizures) who underwent prolonged continuous EEG monitoring; all died *(14)*. Exclusive reliance on this recurrent, discrete electrographic seizure criterion, however, would certainly underestimate the problem of nonconvulsive SE. It establishes a diagnosis beyond question, but exclusion of more continuous discharges is more restrictive a definition than most clinicians will want to use.

There remains a controversy about *continuous* epileptiform discharges. Such discharges have been recorded extremely frequently in conditions that conform well to a reasonable understanding of the traditional definition of SE—which accommodates both continuous and repetitive seizures, as long as there is no recovery between them, i.e., the patient remains in a "fixed and lasting epileptic condition."

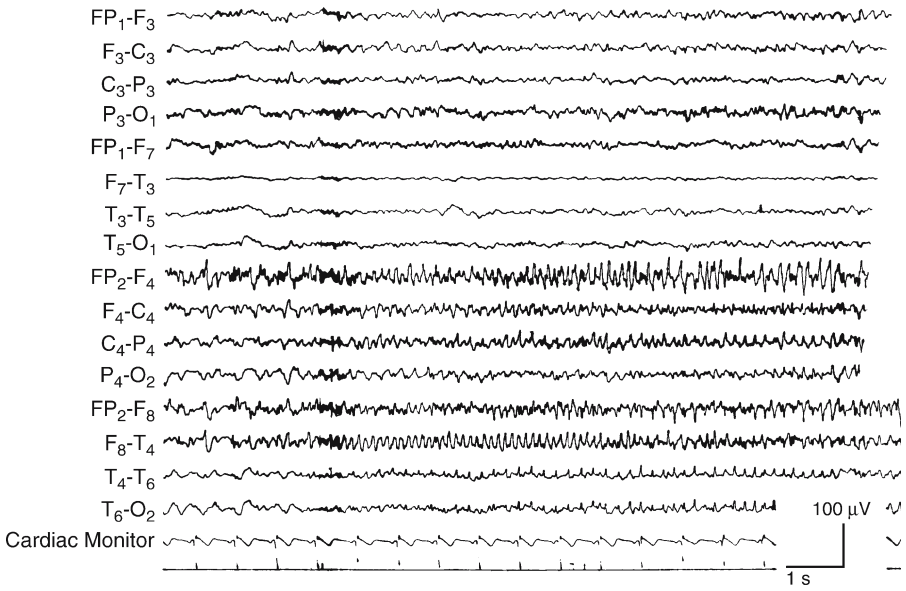

Fig. 1. EEG from a 48-yr-old woman with longstanding epilepsy admitted for cerebral artery aneurysm clipping. She had postoperative focal and complex partial seizures but was not thought to be having seizures at the time of the EEG; she was unresponsive. The EEG showed persistent right hemisphere slowing and three electrographic seizures beginning in the right frontocentral area, each lasting about 30 s. AEDs including pentobarbital were required to stop seizures (left facial twitching clinically), with subsequent excellent recovery.

There are several studies indicating that there is no important clinical difference between patients with intermittent electrographic seizures on the EEG and those with continuous discharges, at least when the discharges are rapid, e.g., ≥1 Hz. In one study of *focal SE* there was no significant clinical difference between patients with intermittent electrographic seizures and those with continuous discharges with a frequency of ≥1 Hz (Figs. 1 and 2) *(15)*. In another series of patients with *clinical convulsions*, intermittent SE had a lower mortality than continuous SE *(16)*. A third study of *all forms of SE* found no difference in outcome between those with continuous and intermittent seizures *(17)*. Overall, continuous discharges may have a somewhat worse prognosis than discrete electrographic seizures and may be better correlated with structural and severe lesions. Nevertheless, the differences are modest, and both EEG patterns indicate serious illness and warrant a diagnosis of status epilepticus.

1.3.2. Characteristic EEG Features of Status Epilepticus

In GCSE, the clinical manifestations make the diagnosis clear. EEG features are detailed in Chapter 5. For nonconvulsive status, clinical features are often subtle and the EEG becomes more important for diagnosis, but the required characteristics are

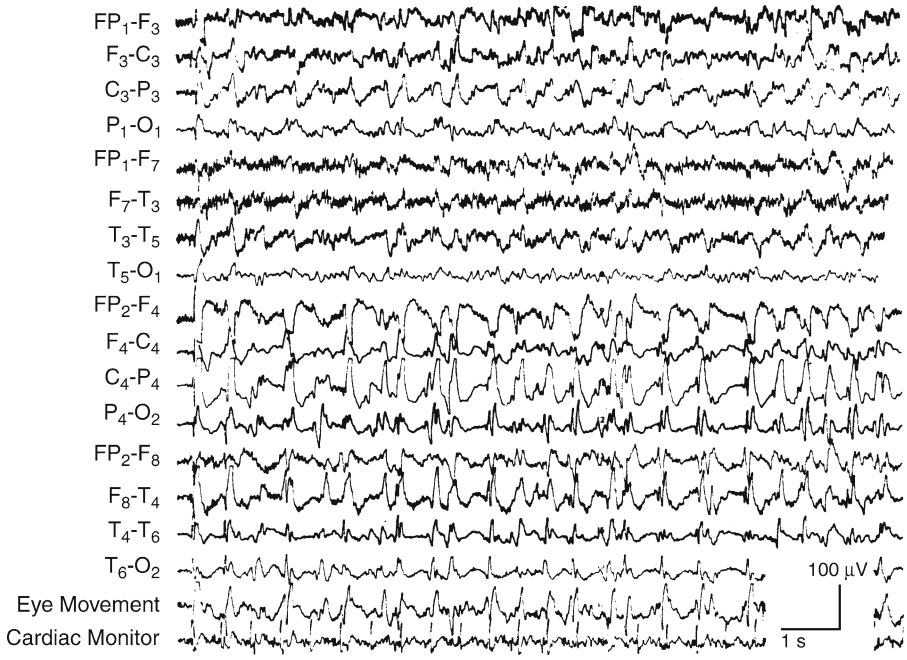

Fig. 2. EEG from a 71-yr-old woman with an old right hemisphere stroke, new infection, and possible theophylline toxicity. Left arm twitching was evident during the EEG. It shows continuous high voltage epileptiform discharges with a frequency of approx 1.8 Hz seen broadly over the right hemisphere. She recovered with AEDs and antibiotics.

more controversial. Common EEG features of almost all definitions of SE include epileptiform spike or sharp wave discharges or slowing, with a rapid, rhythmic appearance. These may be included within two or more electrographic seizures with a discrete onset of typical ictal discharges or with continuous discharges throughout the recording—and always in a patient with some clinical deficit.

Rather than debate what EEG findings *should* be seen with SE, one can be guided by the EEG patterns actually found in patients with a secure diagnosis. Granner and Lee reviewed EEGs from 85 episodes of NCSE in 78 patients with a clinical diagnosis confirmed by EEG and response to AEDs *(18)*. EEG waveform morphologies were quite variable and included typical and atypical spike wave discharges, multiple or polyspike wave discharges, and rhythmic delta activity with intermixed spikes. Discharge frequency was always 1 to 3.5 Hz (mean 2.2 Hz), and only 4% were 3 Hz or faster. Two thirds were generalized and 13% focal, with another 18% generalized with a focal emphasis. In summary, the EEGs in a wide variety of cases of NCSE share three typical features: (1) epileptiform spike or sharp wave discharges or slowing with sharp features; (2) rhythmicity; and (3) recurrence frequencies of >1 Hz.

Logically, these guidelines do not apply to *long interval* periodic discharges, whether lateralized or generalized. Rather, they apply to EEGs with the more rapid

epileptiform discharges diagnosed as epileptic seizures in most clinical studies. Slower discharges constitute periodic lateralized epileptiform discharges (PLEDs) or generalized periodic epileptiform discharges (PEDs), usually not considered SE (*see* section 1.3.4.). Faster discharges would be read by most electroencephalographers as ongoing seizures.

Treiman and colleagues proposed that the EEG in GCSE typically evolves through five characteristic stages *(19)* (*see* Chapter 5). The last two stages are often unaccompanied by convulsions and could be considered either the later phases of GCSE or a type of NCSE. Frequently, there is subtle twitching, blinking, or jerking. Whether these later stages should be considered seizures, or SE, is controversial. Continuous, rapid generalized epileptiform discharges with occasional brief "flat" periods (Treiman's "stage 4") are usually associated with a significant clinical deficit and will be considered NCSE or "subtle" SE by most. Some epileptologists argue that the subsequent, longer interval periodic discharges (PEDs; "stage 5") constitute subtle status epilepticus as well *(19,20)*, but this is not necessarily accepted as evidence of ongoing SE by all *(21)*.

1.3.3. Clinical Correlates of Electrographic Status Epilepticus

Patients with ongoing electrographic seizure activity (continuous or in discrete seizures), usually with minimal or no motor activity, often following earlier generalized convulsions or GCSE or in the setting of severe medical illness (such as anoxia, sepsis, or severe metabolic derangements), have been given several different labels. They have been termed to be in "subtle" SE *(19)* or in electrographic status epilepticus *(22)*. Figure 3 illustrates an example. Some refer to these patients as having "epileptic encephalopathies," indicating that the underlying disease causing the encephalopathy is key and that the epileptic component is secondary and may not respond to AEDs. This term, however, is probably best reserved for certain, primarily pediatric, syndromes (*see* Chapter 16).

Such patients with ongoing discharges on EEG, with no obvious clinical manifestations except diminished consciousness, are not rare. Of 164 patients who had EEGs after apparent control of clinical SE in the large Virginia series, 42% had continued epileptiform discharges, and 14% were considered in NCSE *(23)*. In the VA study of best drug treatments for convulsive SE, 20% of patients whose clinical SE had appeared to stop had evidence of ongoing SE on the EEG *(8)*. Also, among 94 patients with severe head injury, 22% who underwent prolonged, continuous EEG monitoring had seizures, and 6% had SE, all without clinical signs, i.e., they were detected by EEG alone *(24)*. Similarly, 8% of patients with coma of all causes and similar monitoring had NCSE without other clinical signs *(25)*.

Often, it is not clear whether the ongoing repetitive epileptiform discharges are contributing to a clinical deficit or illness. As usual, the outcome is determined primarily by the etiology. Many of these patients have serious cerebrovascular disease or toxic and metabolic encephalopathies or both *(22,26)*. Anoxia and sepsis are common causes, and patients are generally sicker than those with clinically obvious GCSE, in part because it takes time after the initial insult or deterioration to obtain

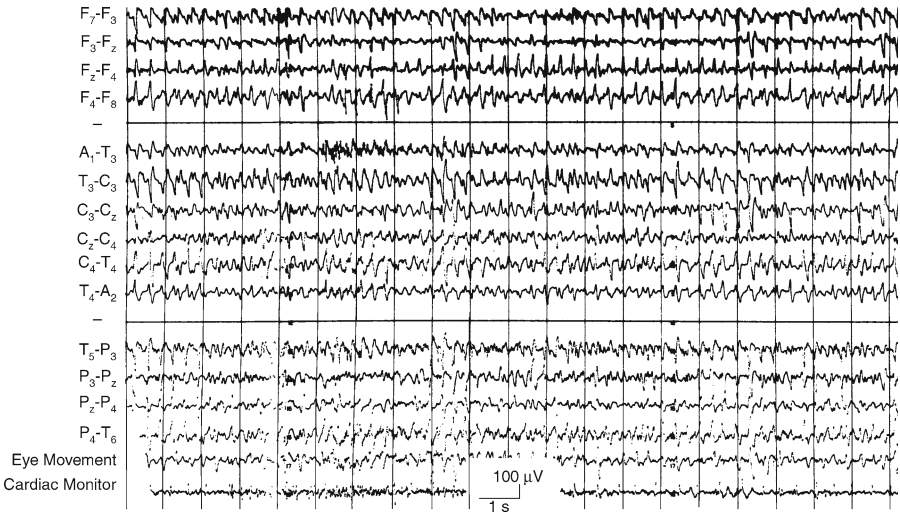

Fig. 3. EEG from an 83-yr-old woman found unresponsive after admission to the medical service with a urinary tract infection and "failure to thrive," with no clinical seizures observed during the hospitalization.

an EEG. Patients who improve from SE quickly usually do not need or have EEGs; those still in SE when the EEG is done are usually the sicker patients.

In several series, these patients have had earlier seizures, were of markedly altered consciousness or comatose, had "subtle" presentations, and were usually unrecognized as being in SE when it was going on. SE often progressed for long durations and had a high mortality—often more than 50%. In one group who all had earlier, recognized clinical SE, EEGs picked up ongoing SE in 24 of 45 patients *(27)*. This "subclinical" SE was far more difficult to treat than clinically evident status, and 24% died. Patients with SE in the setting of serious medical illness have a terrible prognosis, but it is not possible to dissect out that portion of the harm done by epileptiform discharges or NCSE from the damage caused by the underlying illness *(8,22,26–28)*.

Electrographic status epilepticus (ESE; the typical appearance of SE on the EEG, without obvious clinical manifestations) should generally be considered "true" SE for several reasons. First, the EEG discharge appearance, frequency, and rhythmicity are characteristic for many clinical reports *(16,17,22–25,27)* and are similar to those from the study of Granner and Lee (above) *(18)*. Continuous epileptiform discharges with a relatively high frequency (at least 1 Hz, and in some reports 1.5 Hz) have been the primary diagnostic evidence in nearly every case or series report of SE due to some new cause throughout the neurologic literature. As such, these EEGs help to define the usual experience of neurologists treating what they consider to be status epilepticus.

Second, the very large majority of patients with ESE have had clinical seizures recently, and most will have subsequent clinical seizures, indicating that this is not

simply a sign of "burnt out" seizures *(22,26,27)*. For example, patients who develop electrographic SE upon emergence from continuous midazolam or pentobarbital infusions will usually go on to have clinically evident and important seizures *(29,30)*.

Finally, while patients with ESE often have catastrophic neurologic and medical illness, and AED treatment may be unsuccessful in effecting a clinical improvement, a substantial number of patients (particularly those without anoxia) will have an EEG *and* clinical improvement on medication *(27)*. In the end, it makes most sense to consider ESE as a manifestation of status epilepticus and treat accordingly rather than stating that something is not an epileptic seizure because it is difficult or impossible to fix.

Some neurologists are reluctant to diagnose SE in comatose patients with continuous rapid epileptiform discharges, perhaps because such conditions often have disastrous outcomes regardless of the treatment *(8,28)*. The hesitancy discounts the possibility of a patient having two overlapping diagnoses, quite similar to those of cardiac arrhythmias and underlying coronary artery disease. For example, the anoxia that follows cardiac arrest is often devastating, and many such patients have focal or generalized repetitive discrete electrographic seizures without clinical manifestations or with subtle blinking or twitching. They have *both* anoxic brain injury and status epilepticus. The diagnosis of SE is not obviated by the devastation due to the underlying illness. Treatment or reversal of the SE may interrupt epileptic discharges and control subtle clinical motor abnormalities (or even clinical seizures) without improving the overall prognosis. Still, it is no more logical to suggest that these patients do not have SE because they are comatose and have a terrible prognosis than it would be to dispute a diagnosis of infection when antibiotics are not curative.

1.3.4. The Question of PLEDs

Most epileptologists do not consider periodic lateralized epileptiform discharges to be a manifestation of clinical seizures or SE, at least at the time of the EEG. Hundreds of such patients have been studied in several reports *(31–34)*. Clinical seizures occurred in at least 80% before the EEG, and many had prior SE. PLEDs were usually associated with acute, serious focal neurologic illness such as stroke (the most common cause in many reports), tumors, and occasionally infections, metabolic disturbances, earlier epilepsy, and the like. The mortality is high—up to 50% within 2 mo *(35)*. In the largest study to date, PLEDs were certainly a risk for more seizures; half the patients without prior epilepsy who survived the acute illness developed long-term epilepsy *(34)*. Two thirds had SE before the PLEDs. The authors considered PLEDs to be "the terminal phase of status epilepticus," and most epileptologists agree.

Almost all reports of PLEDs show illustrations of EEGs with epileptiform discharges at a frequency of 1 Hz or slower, often every 1 to 2 s and with intervals up to 10 s in some series. EEG features stay fairly constant over a given patient and EEG, but the discharge frequency may decline from one every 1.5 s in the first 2 d to half that frequency a week later, and most PLEDs will resolve after days to weeks

(31). Actual clinical seizures typically show more rapid epileptiform discharges on EEG. The discharge frequency may distinguish between PLEDs and seizures. Most electroencephalographers do not consider PLEDs to be clinical seizures, but most will read EEGs with more rapid discharges (at least >1 Hz and certainly >1.5 Hz) as indicative of ongoing seizures.

The frequency criterion cannot be absolute. One report of seven patients over the age of 60 described recurrent confusional episodes associated with PLEDs—with epileptiform discharge intervals as long as 4 s *(36)*. The clinical deficit and confusion resolved with a slowing of the EEG discharges, whether spontaneous or in response to benzodiazepines. Carbamazepine appeared to prevent recurrences; patients relapsed when it was decreased. The authors considered PLEDs an "unusual status epilepticus of the elderly" in those cases. Another group found classic PLEDs during clinically well-defined SE *(37)*. They demonstrated clearly that PLEDs could be an ictal EEG pattern, although they would not apply the term "status" to patients with longer interval discharges who had no clinical signs of seizures. Anecdotally, some have reported finding PLEDs on a surface EEG and clear rapid seizure discharges in deeper structures on invasive recordings in the same patient.

In summary, PLEDs are strongly associated with acute, severe, focal neurologic lesions. EEG discharges are generally slower than those in typical seizures and resolve with time. PLEDs are generally not considered seizures or SE themselves, but they may be seen during seizures or SE, and their clinical significance differs in individual cases. Clinicians must keep an open mind about rules specifying what is and what is not SE.

1.4. Diagnosis by AED Response

For some, a definition of SE, particularly NCSE, requires a beneficial response of the neurologic deficit to AEDs as a diagnostic criterion. Several papers demonstrate, however, that such a response may be delayed, even up to days *(38–40)*. Many patients with SE and severe underlying medical and neurologic illnesses respond minimally to AEDs, although except in the setting of anoxia it is not possible to know which patients will respond *(8,22)*. This slow (or minimal, or even nonexistent) response makes it difficult to use this criterion for diagnosis at the time of the clinical illness presentation. Many astute clinicians have made the diagnosis of NCSE and treated patients successfully—without waiting for an AED response (or EEG) to confirm the diagnosis. Such cases would be unsuitable for inclusion in many studies, but the right diagnosis was made at the time and appropriate treatment initiated. In the clinical setting one must often make the diagnosis (and persist in treatment for it) for hours or days before an improvement can be demonstrated. Kaplan notes, "Clinical response to treatment is best avoided in defining a syndrome" *(41)*.

There are many ways to establish a diagnosis of status epilepticus. Patients with clear, prolonged clinical seizures and even those with questionable seizures but a definite response to AEDs warrant the diagnosis without much controversy. A response to AEDs may be an appropriate criterion for a retrospective clinical series. In other cases, response to AEDs may be delayed or questionable; the EEG may be

complementary or even the only clear indicator of SE, although it must be in a patient with some neurologic deficit or clinical abnormality.

2. REFRACTORY STATUS EPILEPTICUS

Finally, in terms of labels, refractory status epilepticus (RSE) may be considered the "status of status" or the truly ultimate expression of seizures. It has been defined differently in different settings, with two primary discriminating features. The first typical criterion is duration, variously chosen as 5, 30, or often 60 min of SE *(42)*—even 120 min in some cases *(43)*. As noted earlier, seldom do seizures lasting longer than 10 min cease on their own *(12,13,44)*. Of course, if shorter durations are used, almost all SE will be labeled as refractory. Secondly, some speak of refractory SE as that which continues despite adequate use of one or two (appropriately chosen and dosed) AEDs, usually including a benzodiazepine and at least one longer-acting agent such as phenytoin, fosphenytoin, or phenobarbital *(46,56)*. Indeed, the temporal definitions described above should probably include the same requirement for adequate treatment before declaring refractoriness. Mayer and colleagues appropriately combine these temporal and treatment criteria to include 60 min of SE and inadequate response to a benzodiazepine and one other AED—in appropriate doses *(47)*. The specification of adequate medication is pertinent because patients are frequently treated with insufficient doses, not really warranting a diagnosis of RSE but rather one of "inadequately treated" SE *(48)*.

Refractory status epilepticus is a term usually describing GCSE, but a similar rationale is appropriate for other types of SE. Thirty to 60 min after treatment with two appropriate AEDs in adequate doses is usually reasonable. This is particularly the case for nonconvulsive forms of SE; it is often difficult to be confident about the diagnosis within a shorter time. Of course, if there are ongoing clinical manifestations of seizures (even nonconvulsive, such as blinking or interruption of normal behavior) or EEG evidence of seizures for more than a few minutes without recovery, there is an imperative to treat, long before one can establish a "research" criterion for the definition of SE, refractory or otherwise.

3. CLASSIFICATION

There are many ways to categorize the various types of status epilepticus. In discussing classification schemata, Wolf describes several methods *(49)*. In part, a classification scheme depends on one's goals. One can aim to understand the basic biology, including genetics, of individual syndromes and their relationship to one another. For this purpose, the age-related syndromes of SE described by Shorvon are appealing because presentations and types of seizures and status epilepticus and their biology change, somewhat coherently, with age, especially in the first few years of life *(2)*. Ultimately, better genetic, anatomic, and developmental explanations of seizure disorders and SE will provide a richer intellectual understanding of SE. Neurologists also generally agree that a better biological understanding of a patient's illness will eventually lead to better treatment and outcome.

Basic scientific information and insights, however, are often unavailable at the time of an individual patient's presentation. For more immediate clinical orientation, the organization of this volume parallels the types of status epilepticus differentiated by signs and symptoms seen in clinical practice and, whenever possible, EEG features. The approach to different manifestations of SE syndromes and their management will rely primarily on clinical presentation, with EEG features close behind.

These organizational approaches (biological-genetic and clinical syndromic) are not mutually exclusive, and both will be alluded to. Also, the clinical presentation correlates with the genetic and anatomic substrates and pathophysiology involved. The age and genetic background of the patient should be considered whenever possible. Neonatal and infantile forms of SE are remarkably varied and may have extremely subtle presentations, as covered in Chapters 16 and 17. After infancy, however, childhood and adult forms of SE often appear quite similar, at least in clinical presentations and EEG manifestations.

This book will not advance a comprehensive classification scheme for status epilepticus but rather will focus on the primary clinical and electrographic presentations as they appear to the clinician "in the field." An organization of SE concentrating on its recognition by clinical presentation, symptoms, signs, and seizure types proves convenient for diagnosis and initial treatment. Most of the presentation involves seizure type, but especially with nonconvulsive seizures, this is imprecise, and EEG is crucial in the diagnosis. The stereotyped patterns of clinical and EEG presentations will continue to guide management, treatment, and often, prognosis.

4. TYPES OF STATUS EPILEPTICUS

The largest categories of status epilepticus, and the initial approach to their recognition, involve a determination of focal versus generalized clinical and EEG patterns, and also a distinction between convulsive and nonconvulsive presentations (Table 1). The latter is evident to the examining physician's eye. The former (focal vs generalized) may also be obvious, but particularly with NCSE, focal and generalized presentations may appear identical at some point in the evolution of the status. This is still a useful distinction to make whenever possible because different types of NCSE may have different etiologies, courses, treatments, and prognoses (*see* Chapter 15). The correlation with pathophysiology is imprecise, however, and different etiologies may present with the same type of SE. After early childhood, these types of presentation do not depend substantially on the age of the patient.

4.1. Convulsive Status Epilepticus

Convulsive status epilepticus includes repetitive motor manifestations and comprises three major clinical groups (at least after infancy): generalized convulsive status epilepticus, focal motor status epilepticus, and myoclonic status epilepticus.

Generalized convulsive status epilepticus (GCSE) is the most dramatic, readily recognized, and dangerous form of status epilepticus. Indeed, until the last two decades, nearly all clinical reports of SE covered GCSE alone or did not allow a

Table 1
Different Forms of Status Epilepticus

Generalized	Focal
Convulsive	
Generalized convulsive SE (GCSE)	Focal motor SE
Primary generalized GTC	Epilepsia partialis continua
Secondarily generalized GCSE (focal onset)	
Myoclonic	
Tonic (may actually start as focal)	
Clonic (may actually start as focal)	
Atonic (very rare for SE; may also have focus)	
Nonconvulsive	
Absence (classic)	Other focal with nonmotor features: aphasic, sensory SE
Other generalized nonconvulsive seizures (often secondarily generalized)	Complex partial SE, with prolonged or repeated CP seizures

reader to determine whether other types of SE were included. Although characterized by its generalized convulsions, GCSE actually has some focal onset or focal lesion in most cases *(4,50)*. This is largely because "acute symptomatic" status is often the result of a new stroke or other focal lesion, and "remote symptomatic" status frequently follows an earlier lesion.

Generalized convulsive status entails a significant mortality, typically about 3% from the status itself in adults but 25 to 30% overall because of the usual severity of the underlying illness causing the SE *(4)*. The morbidity and mortality depend tremendously on the etiology. They also depend on age, but this may be a factor not independent of etiology *(51)* and possibly duration of SE *(52)*—although this may be true just for the first few hours of SE.

There is abundant experimental (and lesser clinical) evidence that GCSE can lead to neuronal damage, particularly when prolonged. Experiments by Meldrum and others *(5–7,53,54)* showed that prolonged generalized convulsions with continued electrographic spike discharges for more than 1 h caused neuronal damage in the neocortex, cerebellum, and hippocampus of animals with provoked SE (discussed further in Chapter 9).

Clinically, GCSE also involves substantial morbidity with all the attendant medical and hospitalization complications. Chronic epilepsy may present with an episode of GCSE *(55)*. Thus, status is a risk factor for later epilepsy, but it is less clear that status is the *cause* of the later epilepsy *(55)*. Finally, there is concern for cognitive loss and more lasting encephalopathy due to SE, but this is extremely difficult to be sure of in humans. Consequences of GCSE are detailed in Chapter 6. It is not clear that other forms of SE are as damaging and, accordingly, they may not require exactly the same treatment.

Focal status epilepticus has many manifestations, largely depending on the location of the epileptic discharges in the brain. Focal motor status epilepticus is the most

readily recognized. Nonmotor (or nonconvulsive) forms of focal SE include aphasic and sensory SE and are discussed further in Chapters 7, 10, and 11.

Because of the varied clinical presentations, it is much more difficult to know the incidence, duration, morbidity, and mortality of focal SE (compared to those of GCSE). Though its presentations may be more varied and even interesting, if somewhat less terrifying, than those of GCSE, some large series indicate that focal SE has a comparable mortality *(52)*. In large part, this is due to the focal nature of many acquired lesions such as strokes, hemorrhages, and infections *(56)*. Many of these cases progress from focal SE to involve an alteration of consciousness or even secondarily generalized convulsions. Simple partial SE alone has a lesser but nonnegligible mortality *(57)*. Many other cases, such as SE in benign Rolandic epilepsy, should have a minimal risk of morbidity and mortality *(58)*. As always, etiology is the chief contributor to prognosis.

One extreme form of focal motor status is epilepsia partialis continua (EPC), which may go on for years or even decades even without affecting consciousness or leading to generalized convulsions *(59,60)* (*see* Chapter 7). There is almost always a significant associated neurologic deficit and morbidity, but it is unclear whether the EPC itself causes additional morbidity.

As detailed earlier, few neurologists would consider PLEDs to signify clinical seizures or SE, at least at the time of the EEG recording *(31–34)*. Nevertheless, clinical seizures precede PLEDs in the large majority of cases, and many patients had SE (often focal) earlier. There are some patients for whom it can be demonstrated that a clinical deficit associated with the PLEDs clears with AEDs *(36)* or that PLEDs are associated with definite motor manifestations of SE *(37)*. These cases of PLEDs must be considered SE by virtue of the other criteria for making a diagnosis. When so, they fall under the category of focal status epilepticus.

Myoclonic status epilepticus (MSE) has obvious motor or movement components and cannot be considered nonconvulsive. (Most MSE results from generalized brain dysfunction, but there are cases of focal MSE, sometimes essentially myoclonic EPC.) Clinical presentations may suggest certain causes and preferred treatments, but presentations may also be quite similar over a range of etiologies. As with other types of SE, however, the outcome varies tremendously depending on the etiology (*see* Chapter 6).

The most important etiologic distinction is between those cases of MSE that are "symptomatic" or reflective of an acute and usually severe medical or neurologic illness on the one hand, and those that occur (remarkably infrequently) in more benign idiopathic syndromes such as benign childhood myoclonic epilepsies or juvenile myoclonic epilepsy on the other. Symptomatic MSE often has a grave prognosis, while the idiopathic syndromes are almost always treatable and lead to minimal morbidity or residua. Patients with myoclonic epilepsies of childhood almost always return to their baseline, but in some of these conditions the baseline is not normal (*see* Chapter 17). In yet another group of progressive neurologic illnesses, exemplified by storage diseases, the SE may cease but progression of the underlying disease causes major neurologic deficits and clinical deterioration *(61)*.

Patients with symptomatic MSE tend to do very poorly. Many cases are particularly refractory to medication. Anoxic MSE has the worst prognosis. Many patients with anoxia have EEGs showing electrographic status epilepticus. The minimal or myoclonic clinical manifestations and EEG abnormalities may be suppressible with AEDs, but the underlying illness is determining and almost invariably fatal *(62,63)*. Patients with MSE due to multiple medical problems, such as a combination of uremia and sepsis (a typical cause), also tend to have poor outcomes—certainly determined by the underlying illnesses.

EEG features can help to distinguish between the different etiologic groups of MSE. Some benign genetic childhood myoclonic epilepsy syndromes may include bursts of polyspikes with a relatively normal background. Cases with acute or remote symptomatic causes may show more of an encephalopathic EEG background, and those with the particularly ominous myoclonic status caused by anoxia may show a nearly flat background. The EEG backgrounds in MSE may correlate better with prognosis than do the clinical manifestations.

Infrequently, status epilepticus may assume a *tonic*, or a *clonic*, or an *atonic* form (the last is not actually convulsive, but often prompts falls and injuries). These are mostly neonatal and pediatric cases of SE.

4.2. Nonconvulsive Status Epilepticus

Nonconvulsive status epilepticus (NCSE) has usually been divided into generalized NCSE, characterized by generalized spike and slow wave discharges, and complex partial SE, usually including focal EEG abnormalities and considered the equivalent of prolonged or repetitive complex partial seizures *(64)*.

Diagnostic criteria for NCSE status are frequent topics of debate. Traditionally, the diagnosis involves an abnormal mental status with diminished responsiveness, a supportive EEG, and often a response to anticonvulsant medication. For NCSE overall (without specifying generalized or CPSE), Tomson and colleagues required impaired consciousness for 1 h and an EEG with continuous seizure activity *(64)*, whereas Kaplan sought impaired consciousness for 30 to 60 min with some form of EEG seizure activity *(65)*. Neither required an immediate response to AEDs to make the diagnosis. As noted earlier, a clinical response to AEDs may be delayed up to days *(38,39)*. Often, a diagnosis must be made sooner. When EEG is used to diagnose NCSE, certain features are required, but they can be controversial; almost all studies have in common epileptiform spike or sharp wave discharges or slowing, a rhythmic appearance, and a discharge frequency of at least 1 Hz *(18)*.

Generalized NCSE has often been considered synonymous with absence SE, but this is not accurate. Clinical and EEG manifestations of absence and other forms of generalized SE may be similar (but not identical), and the term "absence status epilepticus" is best reserved for the several varieties of primary generalized NCSE, similar to "status epilepticus in petit mal" described by Schwab *(66)*. It tends to occur in patients with earlier absence or other primary generalized epilepsy, has no features of focal seizures, and includes the typical 3 Hz generalized spike and slow wave discharges on the EEG. Cases of "*de novo* status" are typically generalized on

EEG but unrelated to adolescent absence SE *(67)*. They may occur following medication (particularly benzodiazepine) withdrawal in older patients and appear very similar clinically. Primary generalized NCSE occurs in several idiopathic (usually genetic) syndromes with clinical spells often resembling absence seizures *(68)*. Most forms of primary generalized NCSE are relatively easy to treat and have good prognoses. Unfortunately, there are probably many more cases of secondarily generalized SE. More ominous is the generalized SE diagnosed on EEG in patients with severe, underlying medical or neurologic illness—the patients with NCSE in coma or electrographic SE. Here, NCSE is generalized, but the underlying disease indicates a worsened prognosis.

Focal nonconvulsive status epilepticus, i.e., nonmotor focal SE, is almost certainly markedly underdiagnosed (*see* Chapter 7). The variety of causes, including encephalitis, stroke, mass lesions, trauma, even multiple sclerosis or mitochondrial and degenerative disorders, is matched by the number of clinical presentations, even including atonia *(69),* catatonia *(70),* and anarthria from opercular seizures *(71).*

Complex partial status epilepticus (CPSE) starts focally and involves enough of the brain to alter consciousness. It is the most common form of focal NCSE. It is often a series of prolonged or recurrent complex partial seizures altering consciousness or behavior. It may appear as an "epileptic twilight state" with confusion or bizarre and particularly fluctuating behavior *(72–76)*. At times, there are automatisms. Cases include both prolonged repetitive complex partial seizures and continuous seizure activity. Clinical behavioral manifestations vary remarkably *(77)* (*see* Chapters 10 and 11).

Diagnosis of CPSE has been controversial, and criteria vary markedly from one paper to the next. Early definitions were particularly demanding. Mayeux and Lueders required prolonged complex partial seizures with continuous focal or secondarily generalized seizures on the EEG or repeated complex partial seizures with a focal EEG *(78)*. Treiman and Delgado-Escueta required recurrent or persistent complex partial seizures, fluctuating neurologic signs, recurrent epileptiform EEG patterns, and a prompt clinical and EEG response to AEDs *(75)*. Few patients in more recent surveys would meet these criteria. More recently, Cockerell and colleagues diagnosed CPSE in patients with confusion lasting at least 30 min, with persistent or continuous epileptiform discharges on the EEG, but with no definite requirement of medication responsiveness *(76)*.

The clinical overlap of generalized NCSE and CPSE confuses the classification of NCSE and may explain why reported cases of "absence" (actually, generalized) SE outnumber those of CPSE, even though individual complex partial seizures are far more common than absence seizures in adult clinical practice. Both exhibit confusion or other altered mental status, along with minimal motor activity (except automatisms) and usually no systemic physiologic disturbance. A history of primary generalized epilepsy and rapid, rhythmic, generalized EEG discharges argue in favor of generalized NCSE while a history of focal seizures or other focal neurologic disease suggest CPSE. The key to understanding the overlap is almost certainly that an individual seizure may start focally and generalize rapidly. Cases considered as

"atypical" absence SE may well be complex partial seizures with generalization and prolongation.

The concepts of overlap and progression are buttressed by the correlation of clinical presentation and EEG. Tomson and colleagues studied 32 patients with NCSE, 14 with focal EEG changes (thus labeled CPSE), and 18 with generalized discharges, 6 of whom had primary generalized epilepsy *(64)*. Patients could not be differentiated by clinical features. Similarly, Granner and Lee noted the predominance of generalized EEG discharges in NCSE, but many of their patients had focal discharges on interictal EEGs or after AED treatment *(18)*.

To understand more completely the nature of the illness affecting one's patient and to decide whether prolonged treatment is appropriate (and with what medications), it is helpful to categorize the patient's NCSE precisely. Nevertheless, the clinical manifestations of different syndromes and even some EEG features may be quite similar at presentation, and the initial treatment is often with benzodiazepines for any type. It is important to diagnose NCSE, but it may not be so crucial to determine the NCSE *type* immediately.

4.3. Childhood and Neonatal Status Epilepticus

The general scheme of status epilepticus depicted in Table 1 applies best to patients after early childhood. Neonates and infants develop forms of SE that appear very different clinically and do not fit easily into the categories of focal, generalized, convulsive, or nonconvulsive used for older children and adults. They must be considered separately. Several childhood syndromes are covered in Chapters 16 and 17. The primarily pediatric syndrome of electrographic status epilepticus in sleep (ESES) serves as a useful example *(79,80)*. The EEG patterns warrant a diagnosis of status epilepticus even though the clinical picture at the time may be dominated by sleep. It is clear that the electrographic pattern is related to a serious illness. Similarly, the epileptiform discharges, often rapid and even rhythmic, in an acquired epileptic aphasia, or Landau-Kleffner syndrome (LKS), may reach criteria for SE at times, but the role of repetitive discharges or SE in the progression of the disease is not at all clear. Thus, the diagnosis of SE does not necessarily mandate a particular treatment. The LKS discharges are related to the disease but may not necessitate AED treatment beyond that required to control clinically evident seizures *(81,82)*. In the end, it is difficult to classify many of these infancy and childhood syndromes. An age-related approach may be best in this age group *(2)*. The other SE category headings in this volume should be more useful and appropriate for patients beyond early childhood.

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3

Differential Diagnosis of Status Epilepticus

Pseudostatus Epilepticus

Barbara A. Dworetzky and Edward B. Bromfield

Status epilepticus (SE) is a neurologic emergency that needs to be identified rapidly, with aggressive treatment initiated as early as possible. Many medical and psychiatric conditions can be mistaken for SE, and understanding this differential is one of the most important tasks of the neurologist and emergency department (ED) physician; treating patients for status who do not have it may be harmful. Many individuals present to the ED or intensive care unit (ICU) with sudden and prolonged behavioral change presumed to be SE but ultimately diagnosed as something else *(1–8)*. When patients have motor events that mimic convulsive seizures and a history of "known recurrent status epilepticus" or "poorly treated epilepsy," the bias that these events represent true seizures may be strong enough to compel action early—before history, examination, or laboratory testing clarify the diagnosis *(9)*.

This chapter reviews the differential diagnosis of SE, which can be divided into physiologic and psychologic "imitators." Physiologic imitators are conditions that are neurologically based but not epileptic in origin. They can be divided further into convulsive and nonconvulsive imitators. Convulsive SE imitators are those that involve vigorous, rhythmic motor activity; they are generalized when movements occur on both sides of the body and partial (focal) when they involve one side predominantly. Such events can mimic tonic-clonic, tonic, clonic, or myoclonic seizures. Focal events may also include clonic, tonic, or myoclonic-like components. Nonconvulsive imitators of SE do not have such prominent and repetitive movements. They may be divided into akinetic, atonic, or cognitive-behavioral events. Episodes that imitate nonmotor simple partial SE, experienced by the patient subjectively but not clearly observable by others, are extremely difficult to diagnose unless they fit into another well-described category such as a rapid-cycling mood disorder, panic attack, or psychotic hallucinosis. Psychologic imitators refer specifically to those that are assumed to have a psychiatric origin, either with conscious secondary gain (malingering, factitious disorder) or without these features (conversion, somatization). Psychologic imitators will be termed pseudostatus epilepticus (PSE).

From: *Current Clinical Neurology: Status Epilepticus: A Clinical Perspective*
Edited by: F. W. Drislane © Humana Press Inc., Totowa, NJ

Most patients with a disorder resembling, but not truly constituting, SE have a psychogenic cause for their events, i.e., PSE. Though relatively little has been written specifically about PSE, much more is known about psychogenic nonepileptic seizures (PNES, often preferred to the older term "pseudoseizures")—defined as behavioral episodes that mimic epileptic seizures.

1. GENERALIZED CONVULSIVE IMITATORS (TABLE 1)

As described in Chapter 6, generalized convulsive seizures typically begin with sudden tonic stiffening, followed by repetitive limb jerking. Jerks increase in amplitude and decrease in frequency as the seizure progresses, usually lasting 50 to 120 s. In generalized convulsive SE (GCSE), the convulsive movements become less prominent as this pattern repeats itself *(10)*. Conditions in which there is loss of responsiveness (such as coma or encephalopathy) and associated rhythmic or frequent bilateral body movements likely constitute the most difficult differential for SE. While *convulsive syncope* is one of the most common physiologic imitators of a tonic-clonic seizure, it is never sufficiently prolonged as to mimic SE *(11)*. The analogous but more ominous phenomenon of repetitive myoclonus following cardiopulmonary arrest is likely a form of myoclonic SE (*see* Chapter 6).

Tremors, physiologic or acquired, can be prolonged and may mimic GCSE. Oscillations of the head or limbs are rhythmic and intermittent. Tremors tend to increase with stress and certain postures and disappear with sleep *(12)*. There is often a family history. With preserved consciousness, tremors are usually easy to distinguish from SE, though they can lead to requests for an EEG to "rule out status" for patients in the ICU who have altered consciousness for other reasons.

Certain seizure manifestations indicate basal ganglia involvement, specifically ictal dystonic posturing during temporal lobe seizures, rotatory seizures, and paroxysmal dyskinesia-like seizures *(13)*. *Dystonia* is defined as a fixed abnormal posture caused by sustained muscle contractions. Dystonic reactions can be caused by medications that block dopamine, although tiagabine and other medications have been implicated *(14)*. *Oculogyric crisis*, a dramatic dystonic reaction, can include forced eye deviation along with dyskinesias and other symptoms. It can last 20 to 30 min and is not associated with loss of consciousness *(15)*. *Decorticate and decerebrate rigidity*, such as from hypoxic-ischemic injury, may mimic prolonged seizures. One case report described intermittent decerebrate-like jerks in a 72-yr-old man with a large midpontine stroke from low basilar blood flow *(16)*.

Tetanus, or sustained muscular rigidity as a result of bacterial toxoid, can appear generalized or localized. Early in this illness, the facial muscles are noted to "lock," followed by rigidity of axial and abdominal muscles leading to opisthotonic posturing. Voluntary movement can lead to "reflex spasms" that can occur repetitively. Recurrent brief *tonic spasms* can be seen infrequently in multiple sclerosis and can include nystagmus and convergence spasm. Hyperventilation and hypocalcemia can produce *tetany (17)*, which can lead to prolonged carpopedal spasm and mimic a prolonged focal dystonic seizure.

Table 1
Imitators of Generalized Convulsive Status Epilepticus

Tremor
Dystonia
Rigidity
Tetany
Muscle spasms
Clonus
Shivering
Periodic limb movements of sleep (PLMS)
Restless legs syndrome
Myoclonus

Sustained *clonus* from either brain or spinal cord injury can be elicited inadvertently by a change in posture or limb position and may imitate clonic SE. When the patient is fully alert and conscious and the movement is easily elicited and stopped with rapid limb movement, the diagnosis should be evident. Similarly, *shivering* may imitate clonic SE. Changes in body temperature may be a clue to the diagnosis, but in comatose patients clinical signs are often absent and EEG may be essential to distinguish shivering from seizures. Repetitive flexion movements of the legs or arms during lighter stages of sleep characterize *periodic limb movements* of sleep. They can be associated with *restless leg syndrome* and can keep patients or their bed partners awake at night. Polysomnography is diagnostic *(18)*.

Generalized or multifocal myoclonic SE is common following cardiac arrest. Patients are comatose and may have rhythmic jerks resembling GCSE. Studies of postanoxic comatose patients show that myoclonic status is usually a preterminal condition and not a reversible ictal pattern *(19)*. It consititutes a result rather than a cause of brain damage; this is controversial *(20)*. In anoxic patients who survive, an *action* (or intention-driven) *myoclonus* has been described and has a better prognosis *(21)*. Other forms of myoclonus are seen primarily in infants and young children; they may represent benign or more ominous epilepsy syndromes. When myoclonus occurs in conjunction with opsoclonus, children should be screened for a renal neuroblastoma. EEG can help rule out an epileptic origin of the myoclonus; cortical discharges do not accompany the myoclonic jerks *(22)*.

2. PARTIAL CONVULSIVE IMITATORS (TABLE 2)

Repetitive involuntary movements of a body part may be mistaken for partial or focal motor SE. Rhythmic facial movements, either clonic or tonic, such as those in *hemifacial spasm*, can mimic focal motor SE, or epilepsia partialis continua. These movements, unlike those in most movement disorders, can continue through sleep. The etiology is thought to be arterial compression of the facial nerve at its intersection with the brainstem. *Asymmetric tremor* may be seen in Parkinson's disease and be mistaken for focal motor status, particularly by nonneurologists. *Hypnic myoclonic jerks* at the onset of sleep usually involve the legs, rarely repeat

Table 2
Imitators of Partial Convulsive Status Epilepticus

Hemifacial spasm
Asymmetric tremor
Myoclonic jerks
Palatal myoclonus
Tic disorder
Focal dystonia
Paroxysmal nocturnal dyskinesia
Blepharospasm

over long periods of time, and should not pose a diagnostic dilemma. They have, however, been described as mimicking SE in neurologically impaired patients *(23)*.

Palatal myoclonus, a rare, prolonged rhythmic movement disorder (resulting from damage to Mollaret's triangle in the lower brainstem and cerebellum) can be diminished by sleep or altered with movement or distraction. Examination of the palate usually makes the diagnosis *(24)*. *Tics* are rapid and stereotyped involuntary movements usually involving the face and neck, which can be suppressed by volition momentarily. When they are simple (i.e., not accompanied by complex vocalizations as in Tourette's syndrome), they can be mistaken for myoclonic seizures. Their augmentation with stress and disappearance in sleep is similar to that of many other movement disorders *(25)*. *Episodic focal dystonias*, such as paroxysmal kinesogenic dystonia *(26,27)* or dyskinesias *(28)* can mimic focal motor seizures; their relation to movement distinguishes them from seizures. Interestingly, carbamazepine and phenytoin are used to treat this dyskinesia, so differentiating it from epilepsy may be artificial or at least not critical clinically. Some nocturnal paroxysmal disorders may represent a form of frontal lobe epilepsy, but they rarely present as SE, and when they do, EEG may provide the diagnosis. *Blepharospasm* is a focal dystonia involving the eye muscles. Blinking is noted, and patients report irritated eyes. They may lose vision during forced eye closure. Twenty percent of patients have a unilateral onset. Blepharospasm increases with bright lights and with activity, and decreases with yawning, pinching, and humming *(29)*.

3. NONCONVULSIVE IMITATORS (TABLE 3)

Conditions that produce symptoms lasting more than 30 min, unaccompanied by convulsive movements or epileptiform changes on EEG, will be considered imitators of nonconvulsive status epilepticus (NCSE). Dividing these patients into those who mimic generalized ("absence") or partial NCSE is not particularly useful because this division is primarily by EEG; clinically, they often appear the same. For pseudostatus epilepticus (PSE), the EEG is unremarkable. NCSE imitators will be divided into those that mimic akinetic, atonic, cognitive-behavioral, and nonmotor simple partial SE.

Table 3
Nonconvulsive Imitators

A. Akinetic
Locked-in state
Akinetic mutism
Catatonia
B. Atonic
Periodic paralysis
Cataplexy
Vertebrobasilar "drop attacks"
C. Cognitive, Behavioral, Psychiatric
Encephalopathy
Encephalitis
Paraneoplastic limbic encephalitis
Amnesia
Drug-induced
Transient global amnesia
Dementia
Endozepine-4 stupor
Behavioral change
Temper tantrums
Attention deficit disorder
Self-stimulation
Rage attack
Impulse control disorder
Episodic dyscontrol
Psychiatric disorders
Schizophrenia
Dissociative fugue states
Sleep disorders
Confusional arousal
REM behavior disorder
Kleine-Levin syndrome
Hypersomnia
Nocturnal enuresis
Head banging, rocking
Sleep terrors

3.1. Akinetic Imitators

Arrested movement or speech may be a sign of severe Parkinson's disease, Guillain-Barré syndrome, polyneuropathy, or stroke and are occasionally confused with NCSE. The *locked-in state* refers to paralysis of motor output from a variety of causes, most frequently an anterior pontine infarction. EEG is normal or nonspecifically abnormal, and MRI usually shows the structural abnormality consistent with the diagnosis. The patient appears awake but is unable to respond, except perhaps for opening and closing the eyes.

Akinetic mutism is a rare condition in which a patient appears awake but is unable to respond because of extreme abulia, or lack of motivation to move. It is most often due to bilateral mesiofrontal lesions caused by anterior communicating artery aneurysm rupture, bilateral thalamic strokes, bifrontal neoplasm, or bilateral basal ganglia dysfunction. It can be devastating. It has also been described with drug toxicity, including from phenytoin *(30)*. The lack of fluctuation, abnormal structural studies, and nonepileptiform EEG are all helpful in the diagnosis.

Catatonia is a change in motor output in patients with affective disorder, unrelated to encephalopathy. It may include complete lack of speech, negativism, rigidity, staring, immobility, or agitated excitement and unusual mannerisms or postures, e.g., waxy flexibility *(31,32)*. These mannerisms can also include repeated complex facial movements and may mimic automatisms of complex partial status epilepticus (CPSE) *(33)*. Rarely, catatonia has been reported in true nonconvulsive SE *(34)*.

3.2. Atonic Imitators

Several conditions can lead to sudden collapse, loss of tone, or prolonged weakness and therefore mimic "atonic status," although true persistent epileptic atonia must be extremely rare *(35)*. *Periodic paralysis* is an autosomal dominant disorder with episodes of muscle weakness from either too little or too much potassium. It can occur suddenly after extreme exercise or other stressors. It is diagnosed by abnormal potassium levels during an attack, resolving between attacks.

Cataplexy, a sudden loss of muscle tone, often following strong emotions, observed most often in patients with narcolepsy, can mimic atonic SE. Rarely, attacks can be prolonged, but the association with other symptoms such as sleep paralysis and sudden sleepiness suggest the diagnosis of narcolepsy. Sleep studies can confirm the diagnosis. Vertebrobasilar insufficiency or stroke can present with a sudden *drop attack* but should be diagnosed readily by the associated brainstem symptoms (e.g., ataxia, cranial nerve palsies) and abnormalities on MRI. Manifestations may include "peduncular" hallucinations (nonthreatening complex visual hallucinations), which often reflect distal posterior circulation occipital infarcts rather than lesions in the cerebral peduncles *(36)*.

3.3. Cognitive-Behavioral Imitators

Encephalopathy or coma of nearly any cause, including the postictal state, can be extremely difficult to distinguish from NCSE *(37)*. The EEG helps resolve this dilemma in most cases, although subtle SE can be hard to distinguish from certain encephalopathies. Two specific examples are worthy of mention. The first is herpes simplex encephalitis, a viral infection that causes a subacute behavioral or personality change associated with fever, headache, and focal neurologic deficits including superior visual field defects, aphasia, and hemiparesis. The infection affects frontotemporal structures and often causes focal or generalized seizures *(38)*. The EEG characteristically shows frontotemporal sharp waves or periodic lateralized epileptiform discharges, and MRI can show hemorrhagic frontotemporal lesions. Interictally, patients can be confused, be unable to form memories, have complex

automatisms, and be inappropriate behaviorally. *Paraneoplastic limbic encephalitis* may also mimic NCSE, presenting months before the neoplasm is discovered *(39)*. Patients typically develop difficulties with anterograde and retrograde memory formation, as well as emotional lability, personality change, depression, and anxiety. Seizures are a common comorbidity and may be the presenting feature *(40)*. Both conditions can cause true NCSE but also nonepileptic confusional states.

Amnesia can result from medications, vascular insults, infections, or other causes. Triazolam is the one of the more common culprits and may cause "traveler's amnesia" in individuals who take this benzodiazepine to relax or sleep during travel. Typically, there is amnesia for a period of time related to the travel and associated complex automatic behaviors *(41)*.

Transient global amnesia occurs primarily in the elderly. It presents with a profound, fairly sudden dysfunction of short-term memory *(42)*, often precipitated by an event such as pain, intense emotion, strenuous exercise, or a medical procedure *(43)*. A frequent association with Valsalva maneuver has been noted *(44)*. Typically, patients ask the same questions repeatedly to orient themselves. Alertness and general knowledge are intact. There is both anterograde and retrograde amnesia. Resolution is gradual, although almost always within 24 h. The mechanism is debated and is not felt to be epileptic in most cases. Hypoperfusion, seen in some cases, is more closely associated with an ischemic cause *(45)*.

Dementia, the most common cause of which is Alzheimer's disease, creates one of the biggest clinical challenges by masking epileptic seizures. Memory impairment is gradual over years, and there is decline in other cognitive function. Frequently, though, patients with Alzheimer's disease have episodes of increased confusion related to "sundowning," superimposed infections, or toxicities, and manifest what is termed a "beclouded" dementia. Discrete episodes can be missed, even by the most reliable family member, because the chronic altered mental state allows these behaviors to be viewed as "baseline." On the other hand, memory loss can be caused by seizures *(46)*. Complex stereotyped or habitual movements of the hands, such as tapping or picking, vocalizations such as humming, or empty staring can be difficult to differentiate from the automatisms of NCSE. Subtle myoclonus may also be present, and myoclonic, complex partial, and convulsive seizures may occur, especially in late stages of the disease *(47)*.

Drug side effects are usually too prolonged to be misinterpreted as a single seizure, but they can imitate NCSE or a postictal state. Alcohol intoxication and delirium tremens can produce agitated behavior with confusion and memory impairment similar to that of NCSE. Prescription medications that can produce confusion or alteration in mental state include anticholinergics, antidepressants, antipsychotics, antihistamines, antispasmodics, antiemetics, and antiparkinsonian agents. Drugs that may cause an agitated delirium include benzodiazepines (especially the shorter-acting alprazolam), interferons, histamine 2 receptor antagonists, nonsteroidal antiinflammatories, aspirin, and opioid analgesics. Drugs of abuse that can mimic NCSE include cocaine, lysergic acid diethylamide (LSD), phencyclidine (PCP), ecstasy (methylenedioxyme diamphetamine), mescaline, or psilocybin *(48)*.

True NCSE can occur *de novo* in the elderly, usually in the setting of benzodiazepine withdrawal *(49)*.

Recurring episodes of stupor in adults and in children have been correlated with increased levels of endozepines—endogenous ligands for the GABA-A receptors, analogous to benzodiazepines. Diagnosis is made by finding excessive fast activity on the EEG and increased levels of endozepine-4 in plasma. Intravenous flumazenil, a benzodiazepine inverse agonist, can reverse the episodes and the fast activity on EEG *(50,51)*.

Psychiatric and *behavioral episodes* may also mimic NCSE. In children, *temper tantrums*, manifesting as a sudden behavioral change, may be quite prolonged *(52)*. *Attention deficit hyperactivity disorder* (ADHD) is often the initial impression in children ultimately diagnosed with absence epilepsy *(53)*. ADHD is a developmentally inappropriate and maladaptive inattention, hyperactivity, and impulsivity causing clinically significant impairment in social, academic, or occupational function. Symptoms should begin before age 7 and persist for more than 6 mo in at least two different settings. *Self-stimulation* or stereotyped behaviors in young children and in the mentally retarded population can be accompanied by a dazed appearance, with rocking, swaying, or chewing movements. Similar but more dramatic alterations in behavior can be noted with *rage attacks, impulse control disorder*, and *episodic dyscontrol syndrome*. The difference is that these behavioral episodes are typically more goal-directed and distinguished by the "trigger"—a specific inciting event. Often, these imitators of NCSE are also more easily interrupted by such measures as distraction than is true SE. Occasionally, NCSE can simulate *schizophrenia* and other psychiatric conditions; an EEG can help rule out an epileptic explanation for an atypical presentation of these disorders *(54)*.

Another psychiatric imitator is *dissociative fugue states*, in which a person assumes a new identity, travels a great distance, and has no memory of his or her true identity or how or why he or she has arrived at a destination. These patients often have a history of major personal psychosocial trauma causing posttraumatic stress disorder. The goal-directed and complex nature of the behaviors during the fugue state, such as negotiating ticket purchases and travel, is characteristic.

In addition to psychiatric diagnoses, *sleep-related phenomena* must be included in the differential of NCSE. *Confusional arousals*, consisting of partial wakefulness from delta sleep, are common. Complex motor behaviors without memory or apparent responsiveness to the environment are noted; they include sitting up in bed and speaking unintelligibly. They occur in the first third of the night, during sleep stages I and II. For frequent episodes, long-acting benzodiazepines such as clonazepam can be helpful.

REM (rapid eye movment) *sleep behavior disorder* (RBD) is a condition mostly affecting older men. Patients report motor activity, sometimes fairly aggressive, which can lead to injuries of themselves or a bed partner *(55)*. This condition is more common in patients with neurodegenerative conditions, such as Parkinson's disease and multiple system atrophy, and may be attributed to the absence of the usual atonia associated with REM sleep *(56)*.

Table 4
Imitators of Nonmotor Simple Partial SE

Paresthesias
Negative phenomena
Pain syndromes
Hallucinations
Autonomic disorders
Hypoglycemia
Catechol/histamine disorders
Migraine
Release phenomena
Ocular disorders
Drug effects
Hearing disorders
Psychosis
Vertigo
Anxiety, panic disorders
Posttraumatic stress disorder

Another sleep-related condition is *Kleine-Levin syndrome*. Usually affecting young boys, episodic bouts of hypersomnia, overeating, and sexual disinhibition can last days to weeks. Confusion, hallucinations, and feelings of unreality make this condition difficult to distinguish from true NCSE. Between episodes, patients are usually normal.

Other sleep disorders include *nocturnal enuresis*, which occurs during slow wave sleep and occasionally leads to consideration of a missed epileptic seizure but can also occur in patients who are overmedicated or have obstructive sleep apnea *(57,58)*. Rhythmic movement disorders include head banging or body rocking at sleep onset or during the night. *Sleep terrors* are common in young children but are usually outgrown eventually. A formal laboratory sleep study or polysomnogram with an expanded electroencephalographic montage can help distinguish among non-REM and REM parasomnias and nocturnal seizures.

3.4. Nonmotor Simple Partial Status Imitators

Simple partial status epilepticus (SPSE), or "aura continua," is rare but should be considered in patients presenting with persistent neurologic symptoms in the presence of full, conscious awareness. Prolonged emotional and psychic phenomena, originating in the mesial or basal cortex, can be missed on surface EEG and represent some of the stranger and more difficult-to-diagnose seizures. Nevertheless, simple partial SE can be diagnosed on clinical grounds alone without the EEG, because most patients have similar, time-limited auras that precede complex partial or secondarily generalized seizures at other times. This section discusses imitators of simple partial nonmotor SE (*see* Table 4).

Seizures consisting of bilateral *paresthesias* with preserved consciousness have been reported as part of a simple partial seizure *(59)*. More commonly, such

paresthesias result from cervical spinal cord disease, peripheral neuropathy, or hyperventilation *(60)*. Neurologic examination and ancillary neurophysiologic or neuroimaging studies can usually determine the diagnosis. Hyperventilation can cause focal or generalized paresthesias and a variety of other neurologic symptoms *(61)*. "*Negative" phenomena*, such as paralysis, sensory loss, hemianopia, or amaurosis, usually signs of stroke or other insults, have occasionally been reported as epileptic *(62,63)*. Aphasic SE is unusual *(64–66)* (*see* Chapter 11).

Chronic pain affects millions of people and is responsible for huge medical and disability costs *(67)*. Rarely, pain in the limb, trunk, head, or abdomen has been reported as an ictal phenomenon *(68–70)*. A series of 858 patients with epilepsy found that 24 (<3%) had "painful seizures," 10 experienced unilateral face, arm, leg, or trunk discomfort, 11 had head pain, and only three had abdominal pain *(71)*. Ictal abdominal pain was localized to the temporal lobe, unilateral pain to the contralateral primary somatosensory cortex, and cephalic or head pain was not localizing *(71)*. Another study found that "painful seizures" were due to contralateral parietal discharges *(69)*. "Hemicrania epilepticus" is another form of cephalic SE *(72,73)*. Pain and visual scintillations, as well as other *hallucinations*, can occur with migraine, sometimes in the context of occipital lobe epilepsy. Bizarre eye-rolling movements, head pain, and minimal if any postictal state make this unusual entity confusing diagnostically. Response to medication or other "pure" pain treatment (as opposed to anticonvulsants with concomitant analgesic effects) may distinguish this entity from simple partial SE when the EEG is nondiagnostic.

An *autonomic* simple partial seizure can also become prolonged, manifesting as an umbilical sensation *(74)* or borborygmi *(75)*. Other clinical features of autonomic seizures include shortness of breath, chest discomfort, palpitations, or cardiac arrhythmias; flushing, sweating, or pallor; genital sensations; lacrimation, or pupillary activity; "goosebumps," urinary urgency, or incontinence; and nausea or vomiting *(76)*. *Hypoglycemia*, with tachycardia, diaphoresis, and other autonomic symptoms, may mimic SPSE. Carcinoid, pheochromocytoma, and mastocytosis should be included in the differential diagnosis of SPSE *(76)*.

Olfactory hallucinations are a moderately common epileptic aura of temporal origin, with rare reports of olfactory aura continua caused by an uncinate tumor. More constant disturbances in smell result from a variety of causes including head trauma (with injury to orbitofrontal regions and olfactory groove), meningiomas, neurodegenerative conditions, nutritional deficiencies, migraine, and local nasal pathology (sinusitis, allergies, polyps) *(75)*. Medications and their side effects can interrupt smell and taste; patients often report a "metallic" taste, similar to that in others with olfactory seizures. Gustatory aura continua have been reported *(77)*, with some studies indicating localization to the left hippocampus *(78)*. Though auditory hallucinations (see below) are more common, psychotic visual hallucinations are less stereotyped and are more prolonged than seizures, but they may occur isolated from other psychotic symptoms.

Visual hallucinations can occur as prolonged ictal phenomena of occipital onset and are often associated with postictal headache *(79,80)*. SPSE manifesting as blindness or amaurosis can arise from the parietal-occipital region *(63,81)*. Visual

hallucinations can occur in several different disorders. *Migraine* is probably the most common, with colorful visual flashes noted in a patient's peripheral visual field. "*Release phenonema*" can occur as a result of *ocular disorders* or occipital stroke *(82)*. Optic pathway disturbances from tumors, trauma, or ischemia can produce "phosphenes" or briefs spots of light brought on by eye movement or closure. "Peduncular hallucinosis" can be part of a "top of the basilar" syndrome due to ischemia in the vertebrobasilar territory. Certain *drugs* (e.g., levodopa, digitalis, donepezil, baclofen, fluoxetine) can cause visual hallucinations, as can toxic-metabolic states *(48)*. Hypnagogic hallucinations (visual phenomena noted upon falling asleep) are also recognized as unreal by patients. They are markedly different from the visual aura of migraine, mainly by being much more complex and detailed, although they can trigger migraine *(82)*.

Auditory simple partial SE involving ipsilateral mesiobasal limbic structures can cause "endless repetition of a familiar tune" *(75,83)*. Unilateral buzzing or *auditory sensations,* as from tinnitus, may be confused with simple partial SE, and may be associated with cranial bruits, drugs, or palatal myoclonus. Poor hearing, poor vision, or both can lead to illusions or hallucinations, especially in the elderly *(84)*. Schizophrenia or *psychosis* of any cause can present with auditory hallucinations, but the hallucinations are usually persecutory or self-referential and occur with an otherwise clear consciousness. Vestibular aura, such as *vertigo,* can be epileptic *(75)*. Vertigo, the illusion of movement, often described as spinning, is one of the most common reasons for seeing a neurologist. It is more often a peripheral symptom due to a problem with the vestibular labyrinth *(85)*.

Psychic and experiential auras are among the most interesting and bizarre. Among these are feelings of unreality or strangeness, or conversely, an intense familiarity or déjà vu. Although most epileptic auras last less than a minute, fear, depression, and panic have all been described as a prolonged temporal lobe aura continua *(86–90)*. Mesial temporal lobe seizures may present as *anxiety disorders (91)*. Psychiatric diagnoses such as anxiety, *panic attacks*, depression, and *posttraumatic stress disorder* (PTSD), which also manifest these common symptoms, may thus be considered potential imitators of SPSE. Interestingly, panic disorder, consisting of an intense sudden onset of fear, reaching a maximum within 10 min but usually lasting 15 to 20 min, may be six times more common in patients with epilepsy than in the general population *(92,93)*.

4. PSEUDOSTATUS EPILEPTICUS: THE GREATEST IMITATOR

Pseudostatus epilepticus (PSE) is defined as prolonged or repeated episodes of psychogenic nonepileptic seizures (PNES). Estimates of the incidence of PNES are imprecise, as the few population-based surveys have limitations. The incidence is likely between 1.4 and 4 per 100,000, approx 5% that of epilepsy. Given the typical long duration of the condition, prevalence is higher than incidence—up to 33 per 100,000, with up to 100,000 such patients in the United States *(94–96)*. PNES are much more prevalent in the refractory epilepsy center population, occurring in 10 to 20% of children and 10 to 58% of adults *(97–101)*.

The clinical cost of PNES is substantial *(102)*. It includes chronic overmedication, with roughly 69 to 78% of these patients prescribed large doses of antiepileptic drugs *(103)*, recurrent emergency room visits, testing, and physician visits. PSE likely accounts for a large share of the acute ICU costs in this population. Long illnesses, lower quality of life, and lack of gainful employment contribute prominently *(101,104,105)*.

The proportion of patients with PNES who also have epileptic seizures (ES) is controversial, ranging from 10 to 20% in children and 10 to 50% in adults *(94–97,99,102,106)*. The converse is also significant *(107)*. The task of making a definite diagnosis has been relegated to epilepsy centers with facilities for prolonged inpatient hospitalization, removal of medication, and multispecialty evaluations, including psychiatric. Not all eligible patients are referred for this expensive monitoring or follow-up. Diagnostic accuracy has been reported as between 70 and 90% if results are combined with other predictors *(108)*. When no typical episodes are captured during monitoring, evaluations can remain indeterminate diagnostically.

Misdiagnosis of PNES as ES places patients—especially patients with frequent spells and those that mimic SE—at risk of iatrogenic complications. Up to 38% of PNES patients are admitted to an ICU at some point *(109)*. Ten to 30% of PNES patients eventually present with PSE *(2,110)*. Howell, Owen, and Chadwick reported eight episodes of respiratory arrest in a series of 13 patients with PSE *(2)*. They noted that patients with PSE had other "unexplained illness and deliberate self-poisoning," implying that many had conscious secondary gain problems. Pakalnis and colleagues reviewed 20 cases of PSE where more than half continued to "seize" until they were intubated or had cardiopulmonary arrest *(3)*. The majority received several intravenous anticonvulsants. A single patient with pseudostatus received 27 intravenous cutdowns during emergency treatment *(1)*. PSE can be provoked by induction techniques *(111)*.

Munchausen's syndrome and Munchausen's syndrome by proxy can present with PSE *(4,112)*. Conscious secondary gain, exemplified in malingering and fictitious disorders, has essentially been ignored in this literature. These causes of PNES appear to be much less common than conversion. The possibility of a factitious disorder should be considered even more strongly in cases of possible PSE given the risks of overtreatment.

4.1. Patient Characteristics

Although earlier neurologic disease is not rare in patients with PNES, the major etiologic factors are, by definition, psychologic *(113)*. Psychiatric diagnoses are highly variable, however, and the neurologist often evaluates these patients before the psychiatrist does. Affective, somatoform, dissociative, anxiety, factitious, personality, and psychotic disorders have all been reported although patients often do not fit well into a single category. Any of these diagnoses can include conversion or somatization, i.e., the transformation of emotional into physical symptoms. Of patients diagnosed with conversion disorder, symptoms in 9 to 41% include PNES *(114)*. Knowing the specific psychologic mechanism leading to PNES can be helpful in

Table 5
Ictal Characteristics of Pseudostatus Epilepticus and Complex Partial SE or Generalized Convulsive Status Epilepticus

Seizure Characteristics	PSE	CPSE/GCSE
Onset	Gradual, from waking or "pseudosleep," heralded by pain or trigger	Abrupt, from waking or sleep, painful auras rare
Movements	Out-of-phase, pelvic thrusting, side-to-side thrashing, waxing and waning	Automatisms, in-phase movements, slow before stopping
Eyes	Often closed or fluttering	Usually open, or with clonic blinking or nystagmus
Vocalization	Crying/screaming occasional	Grunt with generalized convulsions; repetitive simple speech with CPS
Responsiveness	Waxes and wanes, some memory for event	Lost suddenly, regained gradually; no memory
Urinary incontinence	Rare	Variable
Injury	Bruises, minor; tip of tongue bite	Facial bone fractures, more serious; lateral tongue bite

guiding treatment. A psychiatrist with experience in PNES is a critical member of the diagnostic and treatment team.

Roughly three quarters of patients with PNDS are women between the ages of 15 and 35 *(95,115)*. Recent studies have turned attention to men and older patients *(116,117)*, in whom inherent biases against diagnosing conversion disorders probably lead to underdiagnosis of PNES. Important comorbid factors include a history of childhood physical and sexual abuse (present in up to 58% of PNES patients), but the reporting of this association is variable *(118)*. Neurologic correlates include a history of head trauma *(118),* mental retardation, or epileptic seizures. Reasonably consistent criteria for distinguishing PNES from ES have been devised, but exceptions are not rare. Using video information without EEG, neurologists accurately distinguished ES from PNES in only 67 to 80% of cases in one study *(96)*.

4.2. Ictal Characteristics

Ictal characteristics of PNES include side-to-side head motions, pelvic thrusting, forced eye closure, emotional outbursts with crying, and subtle trembling movements *(9,103,119–121)* (Table 5). Injury and incontinence, commonly thought to favor the diagnosis of true ES, are less reliable though they may portend an increased suicide tendency *(2,122)*.

Is PSE a distinct clinical entity, or does it represent the end of the continuum of prolonged PNES? The risk of iatrogenic morbidity is clearly increased for patients with PSE, so that recognition of those at risk prior to emergency room presentation may reduce harm. One review found that only 15% of patients with

Table 6
EEG of Pseudostatus Epilepticus and Generalized Convulsive Status Epilepticus

EEG Characteristics	PSE	GCSE
Interictal EEG	Normal or "not definitely epileptiform"	Often epileptiform
Ictal EEG	Normal; artifact obscures	Epileptiform early; artifact obscures during convulsion
Postictal EEG	Normal, awake	Abnormal, slow
Postictal recovery	Rapid, variable	Gradual, variable

PNES had motor phenomena mimicking tonic-clonic seizures. The overwhelming majority were unresponsive without motor manifestations *(103)*. Six of the 35 patients with PNES were treated for SE, however; these were patients with motor phenomena, supporting the idea that motor jerks appear more compelling to treat, and consistent with modern teaching of convulsive SE as a neurologic emergency. Two of the six had respiratory depression, sufficient in one pregnant patient to cause respiratory arrest.

4.3. Diagnosis of PSE

The first requirement for diagnosis of PSE is that the treating physician consider its possibility. The difficulty arises in the ED or ICU setting where suspected SE might trigger a predetermined protocol. Therefore, it is best to attempt a definitive diagnosis before the patient arrives at that facility. The gold standard for diagnosis of PNES is cessation of events after presentation of the diagnosis, including withdrawal of antiepileptic drugs (AEDs), with or without psychiatric intervention. In practice, the determination is usually made on clinical grounds after recording one or more typical events without an epileptic EEG change (*see* Table 6). This is similar for PSE, but there are several caveats.

Not all ES are associated with detectable EEG changes on scalp-sphenoidal recordings. Simple partial seizures may be undetectable in 30 to 80% of cases *(123,124)*, depending on site of origin, duration, number of events recorded, and recording technique. Impairment of consciousness, i.e., progression to a complex partial seizure, however, is accompanied by a marked increase in the sensitivity of scalp-sphenoidal EEG; probably less than 5% of such patients show no diagnostic ictal or postictal features when there is a true epileptic seizure *(125)*. In general, the longer and more dramatic the seizure, the more likely the EEG will show it. Two important exceptions are seizures with excess motor activity obscuring the tracing (mitigated to some extent by experience of the electroencephalographer) and seizures of frontal origin.

Capturing an event on EEG can be done for an outpatient on daytime or ambulatory overnight studies, or in the hospital with long-term video EEG monitoring. For patients with major psychosocial or secondary gain problems, the inpatient setting offers the advantage of viewing any source of rhythmic EEG artifact and learning from the

inpatient team evaluation. Also, AEDs can be withdrawn more safely under supervision. Inpatient monitoring is also superior for patients who may have *both* ES and PNES.

Measurement of serum prolactin or cortisol within 20 min of PNES can help in the diagnosis, although errors can be made in both directions *(126,127)*. PSE affords more time to check this simple blood test. Convulsive SE is nearly always associated with transient hypoxemia and acidosis, and an arterial blood gas may help. Use of induction techniques is controversial, and it is better to obtain a spontaneous event than to induce one, especially with arguably deceptive methods. Some advocate the use of hyperventilation because it is known to bring on some epileptic seizures *(128)*. Patients who are easier to provoke into a seizure are usually highly suggestible and may also have other conversion disorders. It is possible that patients with PSE may be less readily provoked into a spell if conversion is not the etiology *(128)*.

4.4. Treatment

Little is known about the treatment of PSE, or indeed of PNES in general. As in the treatment of epilepsy, the goal is not just to eliminate seizures but to improve overall quality of life. Diagnosis is the basis of treatment. Earlier diagnosis is associated with better treatment outcome *(129)*. The way in which the information is conveyed to the patient by a supportive, caring, and nonjudgmental expert is perhaps the true "art" of this process. Particularly with PNES, where the symptom itself is primarily the expression of an inadequate response to stress, caregivers must address the underlying psychosocial problems.

The process begins with presentation of the diagnosis. We have found it helpful to prepare the patient even before admission by describing the diagnostic problems of patients with intractable seizures, stating that one reason AEDs may be ineffective is that the seizures may not be epileptic or "electrical." We emphasize how common this problem is, and that it is treatable. Further, we prepare all patients, whether PNES is suspected or not, for psychiatric, neuropsychologic, and social work evaluations during the admission for long-term monitoring (LTM). This eliminates confrontation when a "neurologic" explanation is ruled out and the psychiatrist is called in. It also allows for patients who are not ready to confront the possibility of these spells being of nonneurologic origin (perhaps preferentially including the minority who are malingering) to postpone their diagnostic evaluations. Evidence suggests that if patients do not accept the diagnosis of PNES, they are unlikely to be "cured" *(129,130)*. The diagnostic outcome may be improved if patients understand the possible outcomes before monitoring.

Patients with PSE often present more acutely to the monitoring unit during a flurry of "seizures," and it is not unusual that once they are admitted, external psychosocial stressors are reduced and events disappear. The EEG may show nonspecific abnormalities, but by definition they are not epileptic. When the EEG shows epileptiform abnormalities, patients may have *both* PSE and ES. Neuropsychologic testing can be very helpful in explaining common memory complaints and to reveal affective or anxiety disorders that can then be targets for treatment. Patients may be confused or angry when the possibility of PNES is raised, sometimes even more so

in patients with frequent and dramatic episodes such as PSE. Treatment should involve a long-term plan and include contact with outside clinicians if patients allow. Patients with PSE who do not believe the LTM result may go to different treatment centers and remain at risk.

Results of the testing may be discussed whenever data are adequate to make a diagnosis and the patient appears ready to begin assimilating it. As Shen and others have noted *(131),* it is important to emphasize the "good news" that the patient does not have epilepsy, and especially that the team understands that the PNES are involuntary and not "on purpose." Various psychophysiologic effects of stress are mentioned, e.g., its potential to precipitate cardiogenic or noncardiogenic chest pain. If secondary gains are present, alternative means to achieve these ends may be proposed. Also, it is important to provide the positive suggestion that even though the patient does not have control over the events yet, control can be acquired in time, perhaps by a deeper understanding of the psychosocial background or perhaps by techniques such as relaxation training or hypnosis, or by use of more appropriate medications. Patients' suggestibility, sometimes revealed by placebo testing, may be a therapeutic ally here.

Because it takes time to assimilate the diagnosis, this discussion should take place well before discharge. In both the inpatient and outpatient setting, prompt follow-up visits should be arranged with counseling personnel and with the neurologist. The latter is helpful in validating the legitimacy of the disorder and provides important feedback for the practitioner. If the mental health clinician is connected in some way to the primary neurologist, outcome is improved *(132)*.

4.5. Outcome

Most epileptologists have had patients whose PNES ceased merely with presentation of the diagnosis, but this occurs in only a minority. Diagnosis confirmed by LTM has been shown to decrease emergency room visits and cost in general. Inappropriate treatment of PNES and PSE is even more costly than expensive monitoring. One study showed an 84% reduction in seizure-related medical charges in the 6 mo following monitoring *(133)*. Although events declined by 30 to 50%, many patients did not return to work or become "fully functional" *(129)*. With more sustained treatment, as many as 50 to 60% of patients may become episode-free. Good prognostic factors in some studies include sustained psychotherapeutic intervention, female gender, economic independence, employment, absence of coexisting ES, shorter interval since onset of PNES, supportive families, and younger age. Clinical features such as personality disorder, urinary incontinence, and self-injury were poor prognostic indicators. PSE has been a bad prognostic indicator in some series *(134,135)*; it may signify greater psychopathology. One study showed an 80% reduction in the frequency of spells after the use of a provocative technique and advocated using induction to improve outcome *(136)*.

There are several studies of outcome, though none has focused directly on PSE. Patient-based outcome factors include the willingness to accept that symptoms are not due to epilepsy and that the doctor is trying to help. Patients who agree to counseling

are more likely to improve, but this may linked to the belief in agreement about a psychologic problem. Discussing one's own psychopathology and other personal problems can be very difficult. Patients confronted early and directly with the diagnosis, and those who are able to accept it and counseling such as psychotherapy, have better outcomes *(132,137)*. If patients have epilepsy as well, they have to be able to handle uncertainty concerning the news that the current problems are not related to chronic epilepsy. As measured on Quality of Life in Epilepsy (QOLIE) 89 questionnaires, patients with PNES had significantly lower quality of life (lower energy) and worse mood (more depression and anxiety) than patients with ES *(101)*. Patients with pending litigation were less likely to improve. Those with more friends did better *(138)*. Patients do better if they perceive themselves as "healthier" and with better occupational functioning *(130)*.

Physician factors affect outcome as well. Recently, results of a questionnaire given to psychiatrists and neurologists about the accuracy of video EEG for PNES were published. Of neurologists, 70% placed credence in the accuracy of the findings "most of the time" while only 18% of psychiatrists did so *(109)*. Another study reported patient improvement after LTM, but two thirds recurred when the outside physician reinstated the ES diagnosis *(139)*. Reuber and colleagues advocated making as definite a diagnosis as possible and discontinuing AEDs unless there is a clear simultaneous epilepsy diagnosis *(140)*. In a follow-up study of 164 patients with PNES within 4 yr of diagnosis, two thirds of patients with PNES continued to have episodes, and more than half were still collecting Social Security payments; 41% were still on AEDs. Patients with PSE and those already on AEDs were most likely to have delays in diagnosis, mainly from physician factors *(110,140)*. Continuing AEDs supports the belief that the episodes are epileptic and hinders diagnosis and treatment. Widespread use of AEDs for psychiatric purposes has exacerbated this problem.

5. FUTURE DIRECTIONS

Given the relatively poor outcome for patients with PSE, it might be best to predict who is at risk and intervene before presentation. This may decrease the likelihood of iatrogenic harm. Earlier diagnosis may help avoid solidifying incorrect diagnoses. Closer follow-up of patients with PNES may lead to better treatment and reduce recidivism. Training emergency staff to recognize the high rate of overtreatment and iatrogenic harm to patients with PSE may help lead to recognition of the psychiatric presentation. Patients who present to the ED with a history of "known epilepsy with recurrent status" might be identified as a start, because recurrent SE is relatively uncommon in patients with ES *(141)*. Such early interventions may be facilitated by investigating risk factors or clinical characteristics for PSE, as opposed to PNES in general. The importance of early, accurate diagnosis cannot be overstated.

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4
Epidemiology of Status Epilepticus

Elizabeth J. Waterhouse

1. INTRODUCTION

Although prolonged seizure states have been recognized since ancient times, the frequency with which status epilepticus (SE) occurs was not fully appreciated until the last decade. Even in the 21st century, SE continues to challenge clinicians and investigators. Despite recent advances in its diagnosis and treatment, and the advent of sophisticated intensive care units, SE is associated with a persistently high mortality rate. Inpatient medical costs relating to SE have been estimated at $4 billion annually in the US alone *(1)*.

The study of SE presents some methodologic challenges. Patients with SE are not a homogenous population. While SE commonly occurs in those with an established diagnosis of epilepsy, it can also present as the initial manifestation of epilepsy. In addition, it frequently occurs *de novo* in the setting of other systemic and neurologic conditions that may influence its clinical course. The mortality associated with SE has varied according to the reporting site, with lower mortality at an epilepsy center, and higher rates at a university hospital *(2)*. Therefore, the study of SE requires analysis of large populations in order to assess accurately its causes and outcomes. While several epidemiologic studies have looked at its incidence, a comprehensive study of the epidemiology of SE has been conducted in Richmond, Virginia, where SE cases have been identified prospectively for over a decade. This chapter reviews the literature regarding the epidemiology of SE, with emphasis on data from the Richmond SE database.

2. EARLY STUDIES OF SE

2.1. Frequency

Early studies attempting to assess the frequency and other characteristics of SE were hampered by the lack of a standard definition and classification. Most early studies focused on generalized tonic-clonic SE, because it is easily recognized clinically *(3)*. In 1907 Turner reported that 5% of his 380 patients had SE *(4)*. Lennox reported that 10% of 1271 patients he had seen before 1940 had had at least one

From: *Current Clinical Neurology: Status Epilepticus: A Clinical Perspective*
Edited by: F. W. Drislane © Humana Press Inc., Totowa, NJ

episode of SE *(5)*. A number of retrospective chart reviews assessed SE as a proportion of hospital admissions *(6)*. These calculations range from 0.01% of all admissions over a 20-yr period *(7)*, to 0.13% of all casualty visits to a Helsinki university hospital over 1 yr *(8)*, to 3.5% of all admissions to two neurologic intensive care units over an 8-yr period *(9)*.

Not surprisingly, when epilepsy admissions, rather than general admissions, were considered, the rate of SE was higher, ranging from 1.3% *(10)* to 5.4% *(8)*. Rates of SE among all epilepsy patients ranged from 2.3% *(11)* to 10% *(5,12,13)*. Several studies have documented that rates of SE among children with epilepsy are higher than in adults, ranging from 13 to 24% *(14–16)*.

Hauser estimated the incidence of SE in the general population based on a number of factors *(16)*. By summing the following estimates—the number of patients with newly diagnosed epilepsy who present with SE, the number of patients with established epilepsy who develop SE, the annual incidence of febrile SE, and the incidence of SE relating to acute symptomatic seizures—he arrived at an estimate of 180 to 280 persons with convulsive SE per 1 million population per year *(16)*. Shorvon augmented this tally by adding estimates of absence SE, complex partial SE, neonatal SE, nonconvulsive SE, and other SE syndromes, and calculated the estimated total annual incidence of all SE to be about 500 (441 to 646) cases per million in the general population *(3)*.

2.2. Mortality

Early studies of SE mortality focused on convulsive SE, and were limited by problems with case ascertainment, SE definition, and selection bias *(3)*. Series from the 19 and early 20 centuries came from specialized hospital settings, which likely skewed the results toward higher mortality rates. Mortality rates ranging from 10 to 50% were reported *(4,10,17,18)*. SE was a significant cause of death in children with epilepsy and in institutionalized patients *(3)*. Shorvon reviewed 12 case series published between 1970 and 1989 and found overall SE mortality rates ranging from 3 to 11% in children, and 14 to 59% in adults. Totaling the cases in the various studies, the pediatric mortality following SE was 7%, the adult mortality 28%, and the total mortality for adults and children 18% *(3)*. The majority of deaths were attributed to the underlying cause of the SE.

3. DEFINITION

The heterogeneity of cases labeled as SE in the early studies emphasized the need to establish a standard definition of SE. This was the goal of the Working Group on Status Epilepticus convened by the Epilepsy Foundation of America in 1993 *(19)*. The definition agreed upon is "more than 30 minutes of continuous seizure activity, or two or more sequential seizures without full recovery of consciousness between seizures." This definition is used by all the recent epidemiologic studies listed in Table 1.

While this definition has been accepted generally, some argue that the definition of SE should incorporate a shorter duration of seizure activity. These arguments are

Table 1
Results of Seven Population-Based Epidemiology Studies of SE

Location of study	Year published	Reference	*N*	Annual incidence (per 100,000)	Epilepsy prior to SE	Most common etiology	Mortality/ Case fatality rate	Other
Richmond, Virginia	1995 1996	26 39	166	41	42%	Infection/fever (children), Low AED (adults)	22%	Adults and children
Rochester, Minnesota	1997 1998	44 27	184 199	– 18.3[a]	– –	– Acute symptomatic 50%	19%[c] –	Adults and children, retrospective
French-speaking Switzerland	2000	31	172	10.3[a]	43%	Acute symptomatic 63%	7.6%[b]	Adults and children
Hessen, Germany	2001	30	150	17.1[a]	50%	Remote stroke 36%	9.3%[b]	Adults only, mean age 65
California	2002	28	15,601	6.2	Not stated	Late effects of stroke/brain injury 10.8%	10.7%	Convulsive SE only, retrospective: based on discharge diagnosis code
Bologna, Italy	2003	29	44	10.7[a]	39%	Acute symptomatic 48%, CVA 41%	39%[b]	Adults and children

The methods used to calculate the incidence and mortality rates varied between the studies. See referenced articles for methodologic details.
[a]Age-adjusted annual incidence
[b]Case fatality rate
[c]Febrile SE excluded from this study of SE mortality
AED = antiepileptic drug.

based in part on several studies that have demonstrated that the average length of a generalized tonic-clonic seizure is about 60 s and is almost always less than 2 min *(20–22)*. This suggests that seizures lasting longer than several minutes are unlikely to cease spontaneously and therefore may be more appropriately grouped with SE episodes of longer duration. Bleck suggested in 1991 that the definitional duration of SE be shortened to 20 min *(23),* and the VA cooperative trial on the treatment of SE used a definition of 10 min *(24)*. Lowenstein and colleagues have suggested that the definition of SE in adults and older children be further shortened to just 5 min *(25)*.

The appropriate duration for a definition of SE remains controversial. Of course, no one advocates watching a seizing person until the 30-min SE threshold is attained and then initiating treatment. Most physicians treat seizures lasting more than a few minutes, or repetitive seizures, as *impending* SE, with the goal of preventing SE from developing. The clinical goal of early and successful treatment, however, introduces bias into clinical studies of SE. If early treatment is successful, then these cases do not meet the definition of SE and are excluded from studies. Cases that do reach the 30-min minimum duration of SE are those who did not receive or failed early treatment. Studies using the standard definition of SE thus select patients who may be predisposed toward more severe SE and worse outcomes. Research is needed to identify when, during the <30-min ictal episodes, the steep rise in mortality occurs. This is discussed further in Section 11.

4. POPULATION-BASED EPIDEMIOLOGIC STUDIES

The results of recent population-based epidemiologic studies are summarized in Table 1.

4.1. United States

4.1.1. Richmond, Virginia

The Richmond metropolitan area SE study collected data from local private hospitals as well as the Virginia Commonwealth University Medical Center, because data obtained in a tertiary referral hospital may not be representative of SE in a community. In this study, the SE team was notified as soon as SE was diagnosed, and data collection began. Daily admission lists and EEG reports were examined to capture cases that were not reported. It became clear that discharge data (ICD-9 codes) were often inaccurate, and cases of SE were frequently documented with codes for other epilepsy conditions, or not at all. Each case was reviewed carefully to determine whether it met the definition for SE. Prospective collection of data allowed the team to obtain data missing from the chart, particularly with regard to times that SE started and ended (allowing accurate calculation of SE duration), and to obtain accurate descriptions of seizure types.

The incidence of SE in the Richmond, Virginia metropolitan area was 41 per 100,000 individuals per year. The incidences for the pediatric, adult, and elderly populations were 38, 27, and 86 per 100,000 per year, respectively *(26)*. These figures did

not include repeat episodes of SE in a single patient. With validation of the database, it was determined that approx 90% of all SE cases at the university hospital had been identified, compared to only one third of cases in the community hospitals. When underreporting was taken into account, the revised estimate of the incidence of SE in the Richmond area was 61 per 100,000. The overall mortality was 9 per 100,000, with a revised estimated mortality of 17 per 100,000. Extrapolating these figures to the US population yielded an estimated annual national incidence of 152,000 cases of SE and 42,000 deaths associated with SE per year. These numbers underscore the broad scope of SE in the United States.

4.1.2. Rochester, Minnesota

In addition to the Richmond SE study, several large-scale retrospective and prospective SE studies have been published. A retrospective study from the Mayo Clinic, looked at SE in Rochester, Minnesota, between 1965 and 1984 *(27)*. All cases of febrile seizures, acute symptomatic seizures, unprovoked seizures, or epilepsy were reviewed to identify and classify SE. The study identified 199 first episodes of SE during the 20-yr period. The incidence of SE was 18.3 per 100,000. This is considerably lower than the incidence from the Richmond study, likely due to different study methods (retrospective vs prospective), and the differing racial composition of the populations. The majority of the Minnesota study population (96%) was Caucasian, while the majority in Richmond (57%) was African-American. The incidence of SE in Richmond Caucasians was 20 per 100,000, significantly less than that in African-Americans (*see* Section 7). The incidence rates of SE in the Richmond and Rochester studies are comparable when racial factors are taken into account.

4.1.3. California

A study of SE in California focused on generalized convulsive SE only and obtained data by reviewing a state-wide hospital discharge database covering hospitalizations between 1991 and 1998 *(28)*. It relied on ICD-9 coding of convulsive SE, which is subject to inaccuracies because SE is sometimes not recognized as such and may be coded as seizures or epilepsy rather than SE. Thus, the incidence rates in this study are likely to be underestimates. The overall incidence was 6.2 per 100,000 population, and it declined significantly over the 1991–1998 study period, from 8.5 to 4.9 per 100,000. The case fatality rate for incident admissions was 10.7%.

4.2. Europe

4.2.1. Bologna, Italy

A study of incidence and short-term prognosis of SE used prospective surveillance of public general hospitals in Bologna, Italy, and reviewed all epilepsy discharge codes. An annual incidence of 13.1 per 100,000 was found, with the highest incidence in the elderly. The cause of the majority of cases of SE was acute symptomatic illness (48%), with stroke the most frequent etiology (41%). Over one third (39%) of patients reported a history of seizures, and the 30-d case fatality was 39% *(29)*.

4.2.2. Hessen, Germany

A prospective population-based study in Germany identified 150 adult patients with SE over a 2-yr period *(30)*. Patients were reported by neurologists and by intensive care unit and emergency department physicians and nurses. The calculated, corrected, age-adjusted incidence of SE was 17.1 per 100,000, higher in the elderly and in men. Seventy-four percent had a remote or acute brain insult as the etiology, with remote cerebrovascular disease the most frequent etiology, probably contributing to the increased incidence of SE in men and in the elderly. Fifty percent of the patients had a history of epilepsy, and the case fatality rate was 9.3%.

4.2.3. French-Speaking Switzerland

A study of SE in Switzerland collected cases of SE prospectively in 60 hospitals in six French-speaking cantons over a 1-yr period *(31)*. One hundred seventy-two cases were identified by physicians working in hospital emergency rooms, intensive care units, and EEG departments, and by neurologists and pediatricians. The standardized annual incidence rate was 10.3 per 100,000, higher among children under the age of 1, and in the elderly, and higher among men than women. The case fatality rate was 7.6%.

4.3. Developing Countries

There are few large-scale studies of SE in developing countries. Most of the information about SE in African countries comes from case series and cohort studies that suggest that SE is at least as common as in more developed countries. An 11-yr study of SE in Senegal documented 697 cases, with a mortality rate of 24.8% *(32)*. The most common etiology was infection (67%), followed by epilepsy. In Nigeria, 41 cases were diagnosed over a 10-yr period at University College Hospital in Ibadan, with the most common etiology being CNS infection (41%) *(33)*.

Several studies address the occurrence of SE in people with epilepsy. A study at a university hospital in Benghazi, Libya, found that 55 of 568 adult patients had SE *(34)*. One study looked at infantile SE, and found 139 infants treated for SE at two Tunisian hospitals over a 7-yr period. The mortality was 15.8% and the most frequent causes were fever and acute symptomatic diagnoses *(35)*. Several other studies of epilepsy suggest that SE is a common cause of death in epilepsy patients in Africa *(36–38)*.

4.4. Mortality

In most of the population-based studies discussed here, mortality is defined as death within 30 d of SE. The overall mortality of the Richmond study population was 22%, but there was a dramatic difference between pediatric and adult mortality. Pediatric mortality was only 3%, while adult SE mortality was 26%. The elderly had the highest mortality, 38% *(39)*. In the Rochester, Minnesota population, 30-d mortality was 19% following a first episode of SE. Short-term mortality was associated with an underlying acute symptomatic etiology *(40)*. Mortalities and case fatality

rates in other epidemiologic studies ranged from 7.6 to 39% (*see* Table 1). Clinical factors influencing mortality are discussed further in Section 12.

In some of these studies, patients included those admitted to the hospital for SE or epilepsy-related problems, as well as those admitted for other medical or surgical reasons who subsequently developed SE. These two groups may represent distinct subpopulations of SE patients. Hospitalized patients who develop SE *de novo* have an exceptionally high mortality rate of 61% *(41)*. This mortality is not associated with SE duration and may be due to serious comorbid conditions, most commonly recent or remote stroke.

4.5. Time Trends in Incidence and Mortality

In the Rochester, Minnesota population, the age-adjusted incidence of a first episode of SE increased over time from 14.1 per 100,000 between 1945 and 1954 to 18.1 per 100,000 between 1975 and 1984. The increase in incidence was due to the increasingly frequent occurrence of myoclonic SE after cardiac arrest, an uncommon condition in the earlier decades. Before 1965 there were no cases of myoclonic SE in this study. By 1975–1984, approx 16% of SE was myoclonic SE, usually in the setting of anoxic encephalopathy following cardiac arrest in the elderly *(42)*. SE etiologies remained similar over the two decades spanning 1970–1989 *(43)*.

Another potential contributing factor to the increasing incidence of SE may be better recognition of subtle forms of SE. The incidence of "nonmotor SE" increased fivefold between 1935 and 1944 and between 1945 and 1954 and increased modestly thereafter to 2.7 per 100,000 for 1975–1984 *(42)*.

In addition to incidence rates, mortality rates rose over time. Between 1955 and 1984 the mortality increased from 3.6 to 4.0 per 100,000, although the 30-d case fatality rate was unchanged *(42)*. This increase was largely attributable to myoclonic SE. When cases of myoclonic SE were excluded from analysis, SE survival improved during 1975–1984, compared with previous decades *(27,42)*. In contrast, the California study reported a declining incidence of hospitalization for convulsive SE between 1991 and 1998 *(28)*.

5. AGE AND SE

There is a bimodal distribution of incidence of SE, with the highest values during the first year of life and after age 60 (*see* Fig. 1). In adults, the elderly have the highest risk for developing SE, with an incidence of 86 per 100,000 per year *(26)*. Among children 16 yr of age or younger, infants under the age of 1 yr have the highest incidence, 156 per 100,000 per year *(26)*. Other studies have confirmed that the age distribution of SE is U-shaped, with peaks under 1 yr of age and over 60 *(27,28,31)*. Children under age 4 have a high frequency of SE and are more likely than any other age group to have recurrences of SE, usually in the setting of fever or infection *(26,39)*.

Mortality increases sharply with age. Figure 2 illustrates mortality by decade, in 2025 cases from the Richmond SE database *(44)*.

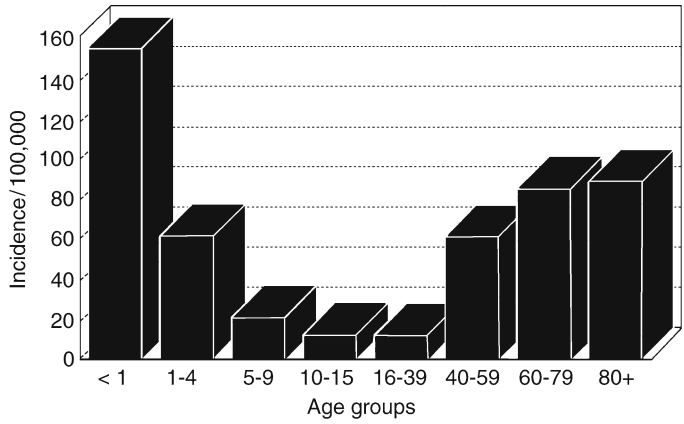

Fig. 1. Age-specific distribution of the annual incidence of a first episode of SE per 100,000 population in Richmond, Virginia. The population for each age group was obtained from the 1990 U.S. Census Bureau for Richmond, Virginia. Reprinted with permission from Lippincott Williams & Wilkins; originally published in ref. *26*.

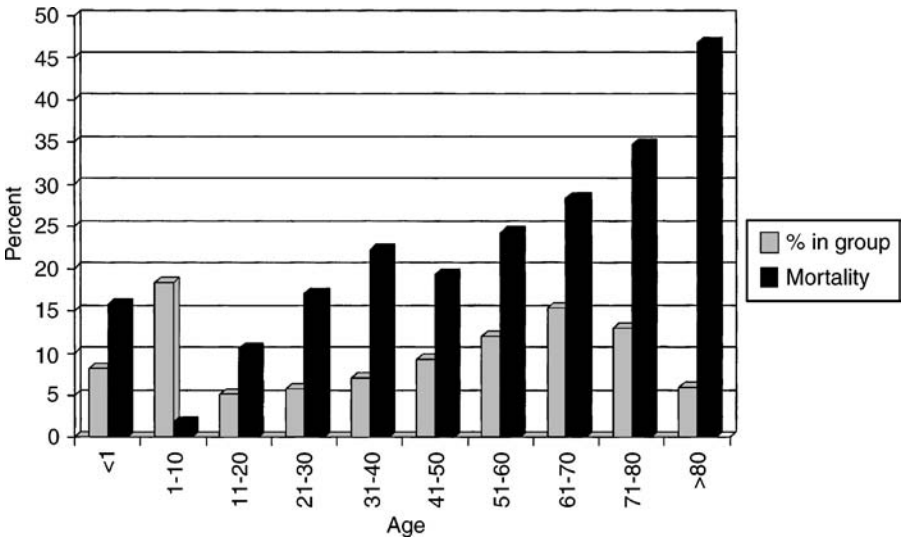

Fig. 2. Age distribution of 2025 patients, by age, in the Richmond Metropolitan Area Status Epilepticus Database. The dark bars denote the percentage of patients who died within each age group.

6. SEX AND SE

There are conflicting reports regarding differences in SE incidence between males and females. In some studies, there were no significant differences *(28,29)*, but others found a greater incidence in males *(27,30,31)*. In Rochester, the incidence of nonfebrile SE was greater among males, partly due to the fact that males had

double the incidence of acute symptomatic and remote symptomatic SE compared with females *(27)*. In Germany, the incidence of SE in males was double that in females, thought to be due to the disproportionately high occurrence of cerebrovascular disease in men *(30)*.

In addition to having a higher incidence of SE, men may also have a higher mortality associated with SE. In the Rochester population, men with SE had twice the risk of death within the first 30 d as women. Even when the analysis was restricted to SE associated with cerebrovascular disease and anoxic encephalopathy in the elderly, the increased risk persisted *(40)*.

7. RACE AND SE

SE incidence rates are higher in African-Americans than in Caucasians. In Richmond, the incidence of SE in Caucasians was 23 per 100,000 and 57 per 100,000 for African-Americans *(39)*. In California, the incidence of convulsive SE (based on hospital discharge code) was 13.35 per 100,000 African-Americans, almost double that for Caucasians (6.94 per 100,000) *(28)*. The incidence of SE is higher in African-Americans in all age groups. The mortality following SE, however, is much lower in African-Americans (17%) than in Caucasians (31%) *(39)*. Race is not an independent predictor of mortality *(45)*.

8. HISTORY OF EPILEPSY

Overall, the majority of patients in most epidemiologic studies of SE do not have a history of epilepsy. As shown in Table 1, the percentage of SE patients with a history of epilepsy ranges from 39 to 50%. In the Richmond study, 42% of the SE population had a history of epilepsy—38% of children, 54% of adults (age 16–59), and 30% of the elderly (over age 60) *(39)*. Patients who had low antiepileptic drug (AED) levels as the etiology of SE (without an identifiable CNS lesion) had a lower mortality (8.6%) than those with an underlying disease associated with SE (32.7%) *(45)*.

9. SE ETIOLOGIES

The etiology of SE is frequently multifactorial, and studies examining SE etiology often tabulate more than one etiology per patient. The most common etiologies in adults in the Richmond study were low AED levels (34%), followed by remote symptomatic events (including old stroke, hemorrhage, tumor, or trauma) (25%) and stroke (22%) (*see* Table 2) *(39)*.

9.1. SE and Cerebrovascular Disease

SE occurs in 1.1 to 1.4% of first-time stroke patients *(46,47)*. In most studies, stroke is a major etiology for SE in adults. When ischemic stroke and cerebral hemorrhages, both acute and remote, are considered together, cerebrovascular disease is associated with 41% of adult SE cases *(26)*. Stroke was also the most common etiology of SE in European studies *(29,30)*. In the California study of

Table 2
Etiology and Mortality for Pediatric and Adult SE Cases

	Adult		Pediatric	
Etiology	% of SE cases	% Mortality	% of SE cases	% Mortality
Anoxia	5	71	0	0
Hypoxia	13	53	5	0
CVA	22	33	10	0
Hemorrrhage	1	0	0	0
Tumor	7	30	0	0
Infection	7	10	52	5
CNS Infect	3	0	2	0
Metabolic	15	30	7	0
LAED	34	4	21	0
Drug OD	3	25	2	0
Etoh	13	20	0	0
Trauma	3	25	0	0
Remote	25	14	38	0
Idiopathic	3	25	5	0

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CVA, cerebrovascular disease; CNS, central nervous system; LAED, low antiepileptic drug levels; OD, overdose.

convulsive SE, the most common etiologies were "late effects of stroke/brain injury" (10.8%), developmental delay (9.9%), sodium imbalance (8.7%), alcoholism (8.1%), and anoxia (8%) *(28)*. A study at a large urban hospital in the 1980s found that AED withdrawal, rather than stroke, was the most common cause of SE in adults, with alcohol-related causes the second most common etiology *(42)*.

9.2. SE Etiologies and Mortality

In adults in the Richmond study, the SE etiologies associated with the highest mortality were anoxia (71%) and hypoxia (53%). Those with low antiepileptic drug levels had a mortality of only 4% *(39)*. In the Rochester population, cerebrovascular disease and anoxic encephalopathy following cardiac arrest were the most frequent causes of SE followed by death within 30 d *(40)*. Other studies reporting low overall SE mortality had a high percentage of patients with AED withdrawal and alcohol-related etiologies *(43)*. Low mortality has been associated with unknown or remote symptomatic etiology *(28,48)*.

9.3. SE Etiologies and Age

Causes of SE differ significantly in the pediatric and adult populations. In children, the most common etiology is infection with fever, present in slightly over half of cases. This was the only pediatric etiology that had any associated mortality—5%. Remote symptomatic etiologies occurred in 38% and low AED levels in 21% of children with SE *(26)*.

10. SEIZURE TYPE

It is difficult to compare the distribution of seizure types in SE studies because each study classified SE differently. The most common seizure type in the Richmond and Bologna studies was partial onset with secondary generalization (42 and 41% of the study populations, respectively) *(29,39)*. In adults, 69% of SE cases had partial onset, and 31% were generalized at onset. Final seizure type was generalized in 74% of adult events *(39)*. The pediatric population had a similar pattern, with 64% of cases having partial onset and slightly more than half generalizing secondarily. Final seizure type was generalized in 71% *(39)*.

Absence SE was uncommon in the Richmond and Bologna populations *(29)*. In the Rochester study, it was also uncommon, but of the six cases, two occurred in adults *(27)*. In two European studies, absence SE was less common than other types, about 6% of SE cases. These studies also had high rates of complex partial SE (26.7 and 43.3%) *(30,31)*.

10.1. Mortality and Seizure Type

When the association between seizure type and mortality was examined, the mortality rate for partial seizures was surprisingly high, at 30.5%. Those with generalized tonic-clonic seizures, including secondarily generalized seizures, had a mortality rate of 20.7% *(39)*. Mortality rates for secondarily generalized SE ranged from 22 to 47% *(29,40)*. Absence SE was not associated with any significant mortality, while mortality following myoclonic SE was as high as 68% *(29,40)*. Seizure type was not a significant independent risk factor for mortality *(40,45)*.

11. DURATION OF SE

Studies using the 30-min minimum for SE duration may have an inherent selection bias. A disproportionate number of patients who did not receive early treatment or were refractory to it are included; these selected patients may be predisposed to longer SE duration, and possibly worse outcomes. Seizing patients who are treated early and respond to treatment, or who stop seizing spontaneously before 30 min, are excluded because they do not meet the definition of SE. Although an SE definition incorporating a shorter seizure duration has been considered, research suggests that there is a definite distinction between these two groups.

Prolonged or repetitive seizures lasting less than 30 min have a very different mortality from those meeting or exceeding the standard 30-min definition of SE *(49)*. The mortality rate for patients with SE was significantly higher (19%) than in those with seizures lasting 10 to 29 min (3%). Interestingly, 42% of the 10 to 29-min seizure episodes resolved spontaneously, and these patients had no mortality. Of the SE cases, only 7% resolved spontaneously, and this subgroup had a mortality of 18%. These findings emphasize the importance of seizure duration as a determinant of mortality and suggest that there may be underlying differences in pathophysiologic mechanisms of shorter versus more prolonged seizures. If the definition of SE included

shorter seizure episodes, SE incidence would increase dramatically, while mortality rate would drop sharply.

Further evidence that duration is a factor affecting SE mortality is provided by another study of the two types of SE described in the earlier definitions: continuous seizure activity versus intermittent seizures without recovery of consciousness in between. This study compared outcomes of patients with continuous convulsive SE and those with intermittent convulsive seizures meeting the definition of SE *(50)*. Those with continuous convulsive SE had a significantly higher mortality (31.4%) than those with intermittent SE (19.6%), suggesting that patients with an increased "ictal burden" have a worse prognosis. It also suggests that the two types of seizure patterns described in the currently accepted definition of SE may represent distinct entities with different implications for outcome.

Most studies have demonstrated that longer duration of SE is associated with worse outcome *(7,43,48)*. Lowenstein and Alldredge found that there was a significant relationship between duration of SE and response to treatment *(43)*. While 80% of patients who received treatment within 30 min of SE onset responded to first-line drugs, the response rate declined progressively with time to treatment. More than 60% of patients in whom therapy was initiated after two hours of SE failed to respond to first-line drugs. There was also an association between longer duration of SE and poor prognosis. This trend was observed for four major etiology groups, and was statistically significant for alcohol-related SE and SE due to CNS infection. Another study found that duration was not a significant risk factor for mortality following SE *(40)*. This study was retrospective, and it is possible that ictal times were not always clearly documented.

In the Richmond population, the mean SE duration was 2 h, and the distribution was skewed toward longer times *(45)*. Mortality for SE lasting less than 1 h was 2.7%, but 32% for SE lasting at least 1 h. After the 1-h threshold was reached, mortality climbed modestly, but when seizure duration was treated as a continuous variable, duration exceeding 2 h was not associated with a statistically significant increase in mortality.

12. DETERMINANTS OF MORTALITY IN SE

Initial clinical studies of SE demonstrated the important contributions of etiology and seizure duration in determining mortality *(14,24,27,40,43,45,51–53)*. Determinants of mortality in SE have been further characterized using multivariate regression analysis. The parameters considered included seizure duration, seizure type, age, etiology, sex, and race. The major determinants of mortality were seizure duration, age, and etiology *(45)*.

Prolonged seizure duration of greater than 1 h was significantly associated with a higher mortality compared to shorter durations, after adjustment for sex, race, etiology, and age.

Age was also a major determinant of mortality, with each additional decade of age associated with an increase of approx 39% in the odds ratio. SE had a higher incidence and a dramatic increase in mortality in the elderly.

Etiology is a major determinant of SE prognosis (*see* Table 2). In the multivariate analysis, anoxia was the only etiology significantly associated with mortality, independently of other variables. Although alcohol-related SE and SE related to low AED levels had low mortality rates, these associations were not statistically significant when confounding variables were taken into account. Clinical SE series with larger numbers of patients in those two categories have demonstrated lower overall mortality rates than have smaller series *(43)*.

The relationship between SE etiology and mortality remains controversial. It has been suspected that the cause of death in SE etiologic groups with high mortality is the underlying disease process rather than SE itself. The relative contributions of prolonged seizure activity and underlying disease process to mortality have not been measured precisely. One study compared stroke patients with SE to a control group of stroke patients without SE who were similar in terms of age, sex, and stroke lesion size. The mortality of stroke patients with SE (39%) was three times higher than that for stroke alone (14%), suggesting a marked synergistic effect of SE and stroke on mortality *(54)*. Further studies are needed to examine the relative contributions of SE itself, and its underlying etiologies, to the outcome of SE.

13. RECURRENCE OF SE

13.1. Correlation With Age

Recurrent SE is more common in children than in other age groups. Overall, recurrent SE occurred in 13% of the Richmond population. Recurrence rates are 17 to 35% in children, 7% in adults, and 10% in the elderly *(26,55)*. Among children, SE was most common in those under the age of 1 yr *(26)*. Of patients under the age of 4, 43% had a repeat episode of SE *(39)*.

13.2. Risk Factors for Recurrent SE

In a study of 95 children with SE, it recurred more frequently in children with idiopathic or progressive neurologic etiologies than with other etiologic categories, and occurred primarily in neurologically abnormal children *(55)*. A study of recurrent SE among all age groups found that it occurred significantly more often in children, females, those with remote or withdrawal etiology, prior seizures, and partial seizures in the setting of coma *(56)*.

14. REFRACTORY SE

SE is usually described as refractory if it persists despite adequate doses of a benzodiazepine and an adequate loading dose of a standard intravenous anticonvulsant (usually fosphenytoin, phenytoin, or phenobarbital). The incidence of refractory SE has been projected to be between 2000 and 6000 cases per year in the United States *(57)*. Refractoriness to first- and second-line treatment occurs in 9 to 31% of SE patients *(24,58,59)*.

Data from the VA cooperative trial of four treatments for generalized convulsive SE confirm that SE is frequently refractory. This study assessed response to

treatment with a loading dose of phenytoin, lorazepam, phenobarbital, or diazepam followed by phenytoin. Patients who did not respond to the first treatment were treated, if necessary, with a second, third, or fourth drug. There was a very high rate of refractory SE, with the majority of nonresponders to initial treatment also failing their second treatments. While 44.5% of those with generalized convulsive SE were refractory to the first treatment, the failure rate for the second treatment was 93%, and 97.7% for the third. There was an even higher rate of refractoriness for those with subtle SE, in whom the success rates were extremely low: first drug 14.9%, second drug 3%, third drug 4.5%, and four or more drugs 27.6% *(24,60)*.

14.1. Refractory SE in Children

Mortality rates for adults with refractory SE are high, ranging from 39 to 48% *(58,61)*. In children, refractory SE is also frequently fatal, with mortality rates of 16 to 43.5% *(62–64)*. Higher mortality is related to young age and etiology, with worse prognosis associated with acute symptomatic etiology and progressive encephalopathy *(62)*. Children with a multifocal or generalized abnormality on EEG at onset of SE had a higher mortality than those with focal abnormalities *(62)*. While longer duration of SE in children is associated with worse outcome, a small case series of seven children with refractory SE requiring prolonged treatment showed that all survived; all had presumed encephalitis *(65)*. Morbidity was substantial—all had intractable epilepsy, and none returned to neurologic baseline.

14.2. Risk Factors for Refractory SE

Few studies have assessed risk factors for refractory SE. A preliminary study of the Richmond, Virginia, population, found that acute CNS etiologies and male sex were independent risk factors for refractory SE, while patients with a history of prior seizure had a significantly lower risk *(50)*. In a retrospective study of 83 episodes of SE at a large academic teaching hospital, 69% continued to seize following administration of a benzodiazepine, and 31% were refractory to treatment with a second anticonvulsant *(59)*. Independent risk factors for refractory SE in this study were nonconvulsive SE and focal motor seizures at onset. Although refractory patients did not have increased mortality, they had a prolonged length of stay and more frequent functional deterioration at discharge *(59)*.

15. SE IN SPECIAL POPULATIONS

15.1. SE in Children

15.1.1. SE Incidence in Children

Among children aged 1 mo to 16 yr, SE is most common in younger children; more than 40% of cases occur in those under 2 yr of age *(66)*. The cumulative incidence of SE was about 1 per 1000 by year of age *(27)*. In the Richmond population the annual incidence of SE in children under 16 was 38 per 100,000 *(26)*. In Switzerland, the incidence was similar for younger children (38.7 per 100,000 in children aged 0–4) but lower for older children (10.9 per 100,000 in ages 5–14) *(31)*.

15.1.2. Etiologies of Pediatric SE

The most common etiologies for pediatric SE are non-CNS infection/fever (52%), remote causes (39%), and decreased AED levels (21%) *(39)*. Etiologies vary according to age, however, with more than 80% of children under the age of 2 having febrile or acute symptomatic etiology, while older children are more likely to have cryptogenic or remote symptomatic causes *(66)*. SE commonly occurs as the initial event in infants with unprovoked or acute symptomatic seizures, more so than for any other age group *(27)*.

15.1.3. Risk Factors for Pediatric SE

In a series of 394 children with SE, 40% had previously documented neurologic abnormalities (21% of those under the age of 2, and 55% of those older than 2). Forty-five percent of the children had a history of earlier seizures—20% of those younger than 2, and 64% over the age of 2 *(66)*. The authors concluded that in younger children, SE occurs primarily in those who are neurologically normal, without history of unprovoked seizures. In older children, SE occurs primarily in those with prior unprovoked seizures, who are often neurologically abnormal.

Epilepsy is an important risk factor for SE in children. Ten to 20% of patients with epilepsy will have an episode of SE *(67)*. In a population-based cohort of children with epilepsy in Finland, 27% had an episode of SE. Risk factors for SE included remote symptomatic cause, age of epilepsy onset 6 yr or younger, and partial seizures *(68)*.

15.1.4. Seizure Characteristics

Generalized convulsive seizures are the major seizure type for pediatric SE, constituting about two thirds of SE in children *(67)*. Not surprisingly, seizure type is correlated with etiology, with febrile SE having the highest proportion of generalized seizures, followed by remote symptomatic and acute symptomatic SE *(27,69)*. Children under the age of 1 yr are more likely to have SE lasting more than 2 h than briefer episodes *(27)*.

15.1.5. Mortality

In general, the morbidity and mortality associated with SE in children are low and are primarily a function of etiology *(66,70)*. The overall mortality of SE in pediatric patients is 0 to 10% *(14,15,69,71,72)*, dramatically lower than that in adults or the elderly. In the Richmond population, the mortality rate for SE in children was 2.5%. The etiology in all children who died was non-CNS infection *(26)*. The occurrence of SE did not alter the mortality rates of children with epilepsy *(68)*.

15.1.6. Febrile SE

Febrile seizures occur in 2 to 5% of children in the US and Western Europe *(70)*. Case series suggest that about 4 to 5% of childhood febrile seizures last at least 30 min and thus qualify as SE *(70,73–79)*. Febrile SE comprises more than 50% of all SE in children. It is most common under the age of 4 yr *(26,27,70)*.

In a study of 180 children with febrile SE, 74% presented with SE as the initial febrile seizure *(70)*. Febrile seizures were usually generalized (65%), and the majority lasted less than 1 h.

Early studies of childhood febrile convulsive SE portrayed a generally poor outcome, with significant morbidity and mortality *(3)*. Three large-scale population-based studies of febrile seizures, however, have presented a much more optimistic outlook, with no mortality in the 2740 children studied *(73,75,76)*. In a recent study comparing children with febrile SE to children presenting with a first febrile seizure, risk factors for febrile SE were neurologic abnormality, history of neonatal seizures, and family history of epilepsy *(70)*.

15.2. SE in Twins

Several population-based studies have examined the occurrence of epilepsy in twins and found that genetic factors play a role in the expression of epilepsy and febrile seizures *(80–82)*. A study of 8681 twin pairs in the Virginia Twin Registry found that 13 pairs of monozygotic and 26 pairs of dizygotic twins included at least one twin with a history of SE *(83)*. In three of the monozygotic twin pairs there was a history of SE in both twins; none of the dizygotic twin pairs were concordant for SE. The frequency of SE among the monozygotic twins of individuals with SE was more than 90 times that observed among registry twins overall. The calculated SE concordance rate was significantly higher for monozygotic than dizygotic twins, suggesting that genetic factors are involved in determining the risk for SE.

15.3. SE in the Elderly

15.3.1. SE Incidence

SE is an important neurologic concern in the elderly population, with an incidence rate in the Richmond study of 86 per 100,000 per year, almost twice that in the general population *(28,39)*. In the German study there was an even more dramatic increase in SE incidence in the elderly—54.5 per 100,000 over the age of 60, compared with 4.2 per 100,000 in adults aged 18 to 59 *(30)*. In the Richmond study, the elderly population was further subdivided into age groups of 60 to 69 yr of age, 70 to 79 yr, and >80 yr. Each of these subgroups demonstrated an incidence of more than 80 cases of SE per year per 100,000 individuals, but the highest incidence was in the 70- to 79-yr-old subgoup—100 per 100,000 individuals per year *(84)*. Almost 0.4% of people who survive to age 75 will have had an episode of SE *(27)*.

15.3.2. SE Etiologies in the Elderly

Although the elderly have a variety of etiologies of SE, the majority of cases are related to stroke, either acute or remote *(11,84–86)*. In the Richmond study, the most common etiologies of SE in the elderly were: stroke 21%, remote symptomatic 21%, low AED level 21%, hypoxia 17%, metabolic 14%, alcohol-related 11%, tumor 10%, infection 6%, anoxia 6%, hemorrhage 5%, CNS infection 5%, trauma 1%, idiopathic 1%, and other 1% *(84)*. The majority of cases in the remote symptomatic category had prior strokes. When remote symptomatic strokes are combined with acute stroke cases, stroke is an etiology for SE in 61% of the elderly cases *(26)*.

Other studies have confirmed that cerebrovascular disease is the major cause of SE in the elderly. In Germany, remote stroke was associated with 36% of SE patients

and acute stroke with 14% *(30)*. The California study found that the most common medical condition associated with convulsive SE in the elderly was late effect of stroke or brain injury *(28)*. The Rochester, Minnesota study suggests that another common category of etiology for SE in the elderly is dementia *(27)*.

15.3.3. SE Mortality in the Elderly

It is likely that the increased risk of stroke, metabolic abnormalities, and progressive conditions in the elderly predispose them to SE and contribute to its high mortality. The mortality rate for SE in the elderly (60 and older) is 38%. The very old elderly (80+) have a mortality of about 50% *(26,39)*. Etiology is a strong determinant. SE in elderly patients with anoxia had an almost 100% mortality, while metabolic disorders, systemic infections, CNS infections, hemorrhages, tumors, hypoxia, stroke, and head trauma each had at least a 30% mortality. Low AED levels, alcohol withdrawal, and idiopathic etiologies each had a mortality of less than 6%. Remote symptomatic cases (mostly prior strokes) had a mortality rate of 14% *(84)*.

15.3.4. Seizure Types in the Elderly

Seizure types in the elderly in the Richmond study were: partial seizures 29%, partial with secondary generalization 45%, generalized tonic-clonic seizures 26%. Generalized seizures had the highest mortality (49%), with mortalities of 30% for partial seizures and 36% for secondarily generalized SE. The majority of elderly patients (56%) had no prior history of SE, but those who did have previous seizures had a significantly lower mortality of 25% *(84)*.

Nonconvulsive SE (NCSE) is a common presentation of SE in the elderly and may be challenging to diagnose. A small, prospective series of elderly patients with NCSE due to stroke, hypoxia, head trauma, tumor, hyponatremia, electroconvulsive therapy, and epilepsy concluded that NCSE has a worse prognosis in the elderly than in younger patients *(87)*. This difference in outcome was attributed to the severity of underlying etiologies in the elderly, and because of hospital-acquired infection, which occurred in seven patients and caused death in three. A study of 25 cases of NCSE in critically ill elderly patients (excluding those with anoxic encephalopathy) found a 52% mortality. Death was associated with the number of acute life-threatening medical problems on presentation *(88)*.

16. SE IN THE ICU

There are two categories of SE patients in the intensive care unit: those who are transferred or admitted to the ICU because of SE, and those who are there because of severe medical or surgical illness, in whom SE is diagnosed *(89)*. The latter present the diagnostic challenge—despite severe metabolic, neurologic, or systemic problems that predispose these patients to SE, NCSE may remain undiagnosed unless an EEG is obtained. Eight percent of comatose ICU patients who had no obvious clinical signs of seizure activity were found to have electrographic SE on EEG, emphasizing the importance of this test in evaluating comatose patients *(90)*.

Even in patients in whom SE is easily diagnosed due to obvious generalized convulsive seizures, it is important to obtain an EEG. NCSE may continue after clinical seizures have stopped. In the Richmond population, 14% of patients who stopped seizing clinically demonstrated persistent electrographic SE on EEG, and 34% had recurrent seizures, of which more than two thirds were nonconvulsive. In a study of patients with generalized electrographic SE, 40% had been diagnosed with clinical SE and were thought to have stopped seizing *(91)*.

17. CONCLUSIONS

Epidemiologic data suggest that SE is a surprisingly common neurologic emergency. It occurs most frequently at the extremes of life—in the very young, in whom fever or infection is the most common etiology, and in the elderly, in whom SE is most often associated with acute or remote stroke. While the mortality following SE in children is very low, mortality rates climb significantly for the elderly. The independent determinants of mortality following SE are age, seizure duration, and etiology. The alarmingly high overall mortality rate emphasizes the need for rapid recognition and treatment of SE.

ACKNOWLEDGMENTS

The author gratefully acknowledges the assistance of Lynne Penberthy, MD, MPH, Linda Garnett, RN, Cynthia Cors, MS, Viswanathan Ramakrishnan, PhD, and Ms. Elizabeth Seitz in the preparation of this chapter. The Richmond, Virginia Status Epilepticus Study is supported by NIH Grant PO1-NS25630.

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5

The Electroencephalogram in Status Epilepticus

Susan T. Herman

1. INTRODUCTION

Status epilepticus (SE) occurs when a continuous epileptic seizure lasts for more than 30 min, or intermittent epileptic seizures recur without intervening recovery to baseline neurologic function *(1)*. For practical clinical purposes, 10 min of continuous seizure activity is often used as a criterion for diagnosis of SE *(2)*. While most cases of convulsive SE are easy to diagnose by clinical criteria alone, the electroencephalogram (EEG) is an essential tool for the diagnosis and classification of nonconvulsive SE (NCSE). EEG is also valuable in classifying SE and in monitoring the response to therapy. The clinical manifestations and treatment of SE are discussed thoroughly in other chapters; this chapter will focus on the electrographic patterns of SE and the utility of EEG for diagnosis, classification, and management of SE.

There are as many forms of SE as there are different types of epileptic seizures *(3)*, and the EEG manifestations of SE vary widely. A classification scheme paralleling the International League Against Epilepsy Classification of Epileptic Seizures *(4)* is reasonable. Classification of SE by EEG patterns yields three main groups: (1) SE that begins focally, with or without secondary generalization; (2) SE that is generalized at onset; and (3) SE that has both focal and generalized features or is otherwise poorly classified. This grouping, however, has several limitations. First, EEG initiated in the middle of SE may be unable to distinguish between focal and generalized SE. Second, this classification system fails to separate SE with potential for irreversible neuronal injury from that in which outcome is nearly uniformly good. Both generalized convulsive SE (GCSE) and absence SE (ASE) are classified as generalized, although they can have widely disparate outcomes. Third, no clinical or historical information is incorporated into the classification, limiting its bedside utility. A more practical EEG classification scheme, outlined in Table 1, first separates SE into convulsive SE (clinically obvious, EEG not usually required for diagnosis) and nonconvulsive SE (inconclusive clinical signs, EEG often required for diagnosis). Within each broad group, SE can be further subcategorized into generalized or partial by EEG criteria.

From: *Current Clinical Neurology: Status Epilepticus: A Clinical Perspective*
Edited by: F. W. Drislane © Humana Press Inc., Totowa, NJ

Table 1
Classification of Status Epilepticus by Seizure Type

1. Generalized convulsive SE (GCSE)
   1.1. Generalized onset
      1.1.1. Primary generalized tonic-clonic SE
      1.1.2. Clonic SE
      1.1.3. Tonic SE
      1.1.4. Myoclonic SE
   1.2. Partial onset
      1.2.1. Secondarily generalized tonic-clonic SE
2. Nonconvulsive SE (NCSE)
   2.1. Generalized onset
      2.1.1. Generalized absence SE (ASE)
         2.1.1.1. Typical
         2.1.1.2. Atypical
      2.1.2. Subtle or electrographic generalized convulsive SE (SGCSE)
   2.2. Partial onset
      2.2.1. Simple partial SE
         2.2.1.1. Epilepsia partialis continua (EPC)
      2.2.2. Complex partial SE
      2.2.3. Electrographic partial SE
3. Age-related SE
   3.1. Neonatal SE
   3.2. Electrical status epilepticus during slow sleep (ESES)
   3.3. Landau-Kleffner syndrome
4. Nonepileptic status epilepticus (psychogenic or pseudo-status epilepticus)
5. Controversial patterns
   5.1. Periodic lateralized epileptiform discharges (PLEDs and PLEDs plus)
   5.2. Bilateral independent periodic epileptiform discharges (BiPLEDs)
   5.3. Generalized periodic patterns (GPEDs)
   5.4. Triphasic waves
   5.5. Burst suppression

Most of the controversial EEG patterns occur in patients with NCSE. Partial or focal NCSE shows ictal onsets with a single topographic EEG maximum, followed by evolution in distribution, amplitude, and frequency. If SE is discontinuous, background activity between seizures is typically slow and disorganized with occasional focal interictal epileptiform discharges (IEDs). Generalized NCSE shows continuous or cyclic generalized repetitive or rhythmic spiking that waxes and wanes in amplitude and frequency. Some discharges are followed by electrodecremental suppression of background activity. Finally, bihemispheric NCSE has features of both focal and generalized SE. Some bihemispheric EEGs show discrete electrographic seizures with widespread fields that are more pronounced over one hemisphere but may shift between hemispheres at different times during the recording. Others show waxing and waning cycles of asymmetric bihemispheric spike-and-wave discharges.

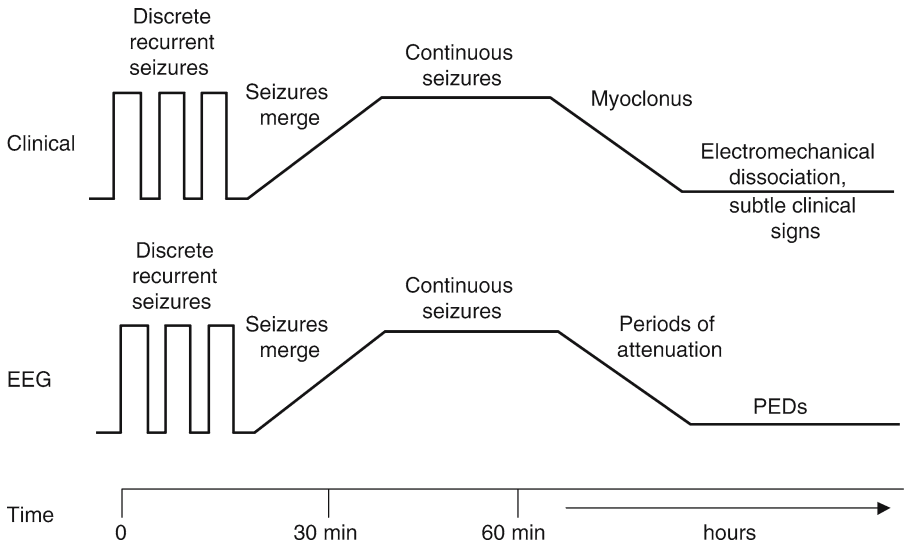

Fig. 1. Schematic of clinical and EEG changes during SE. Initial discrete seizures merge into continuous ictal discharges. Over time, ictal discharges become discontinuous, separated by periods of severe diffuse background attenuation. Clinical manifestations cease or become subtle but discontinuous ictal EEG discharges continue, eventually becoming periodic epileptiform discharges (PEDs). This sequence occurs in experimental animals and some cases of human SE, but may be modified by underlying illness and treatment. Adapted from ref. *105*.

Unfortunately, the EEG pattern at any one time may not be able to distinguish between focal and generalized NCSE, as seizures that begin focally may evolve to more widespread or generalized patterns *(5)*.

EEG patterns in status epilepticus undergo evolution over time, often paralleling changes in clinical manifestations (Fig. 1). Sequential EEG changes, such as decreased duration of ictal discharges and increase in intervening background attenuation, represent progressive neuronal dysfunction *(6)*. As the EEG deteriorates, typical motor clinical manifestations become more subtle or disappear entirely. Evolution of the EEG depends on the baseline condition of the patient, time from SE onset, etiology, and treatment. Such changes make classification of SE based purely on EEG criteria more problematic.

2. EEG CRITERIA FOR STATUS EPILEPTICUS

To qualify as SE, EEG ictal discharges should be continuous or recurrent for more than 30 min without return to a normal clinical state or a preictal EEG pattern between seizures. Generalized convulsive status epilepticus and recurrent discrete focal or generalized seizures with frequencies greater than 3 Hz are usually easily recognizable, but diagnostic criteria for invariant patterns and discharges slower than 3 Hz are more controversial *(7)*. Even experienced electroencephalographers

Table 2
EEG Criteria for Status Epilepticus *(7,8)*

Continuous or recurrent ictal discharges lasting more than 30 min without return to preictal EEG or clinical state:

A. Recurrent ictal discharges (requires 1–4, with or without 5)
1. Repetitive or rhythmic generalized or focal spikes, sharp waves, spike-and-wave or sharp-and-slow-wave complexes, or rhythmic waveforms with frequency 3–20 Hz
2. Discharge duration >10 s
3. Paroxysmal change from baseline EEG activity
4. Evolution in amplitude, frequency, and/or field
5. Postictal focal or generalized slowing or voltage attenuation

B. Continuous (>30 min) ictal discharges

Frequencies >3 Hz: same as above

Frequencies <3 Hz (requires 1–3, with or without 4)
1. Repetitive or rhythmic generalized or focal spikes, sharp waves, spike-and-wave or sharp-and-slow-wave complexes, or rhythmic waveforms
2. Gradual evolution in voltage, frequency, and/or field
3. Significant improvement in clinical state or EEG after intravenous antiepileptic drug
4. Postictal focal or generalized slowing or voltage attenuation

frequently disagree as to whether a particular EEG pattern represents SE, and the medical history, clinical state of the patient, and response to antiepileptic drugs (AEDs) may be required to make an accurate diagnosis. Several investigators have developed criteria to improve the diagnosis of nonconvulsive or electrographic seizures *(8,9)*, which are summarized in Table 2. These criteria, however, are not universally accepted.

The significance of an EEG response to AEDs is also debated. Intravenous benzodiazepines may abolish electrographic seizures, but may also suppress triphasic waves *(10)*. Therefore, improvement in the EEG alone after AED treatment does not prove that a particular EEG pattern was a seizure. A controversial EEG pattern is confirmed as ictal only when marked clinical improvement occurs in conjunction with EEG improvement. Comatose or obtunded patients rarely show an immediate and definitive clinical response, even if EEGs improve. Thus, many EEG patterns remain ambiguous.

3. SPECIFIC EEG PATTERNS IN STATUS EPILEPTICUS

3.1. Generalized Convulsive Status Epilepticus

3.1.1. Generalized Onset

3.1.1.1. Primary Generalized Convulsive Status Epilepticus

Primary generalized convulsive status epilepticus (GCSE) is relatively rare, usually occurring as a result of antiepileptic drug noncompliance or alcohol withdrawal.

Primary generalized tonic-clonic seizures (GTCS) show bilaterally symmetric behavioral and EEG manifestations from onset, and progress through a stereotyped sequence of clinical and EEG manifestations *(11)* (Fig. 2). The initial tonic phase shows sudden diffuse voltage attenuation with superimposed very-low-amplitude fast frequencies (generalized paroxsymal fast activity; GPFA) at 20 to 40 Hz. Generalized rhythmic activity gradually increases in amplitude and decreases in frequency to approx 10 Hz (the epileptic recruiting rhythm), and then to theta and alpha activity with intermixed slow waves. Many of the initial EEG rhythms may be partially obscured by diffuse muscle activity. During the clonic phase of the seizure, bursts of polyspike-and-wave activity and electromyographic (EMG) activity occur synchronously with clonic jerking. In continuous primary GCSE, this clonic phase continues for the duration of the SE attack. In GCSE characterized by repetitive GTCS with impaired consciousness, the intervening EEG shows diffuse slowing, voltage attenuation, and disorganization. Generalized epileptiform discharges may be present between seizures. Although repeated seizures diminish in duration and intensity over time *(11,12)*, progression to subtle generalized convulsive status epilepticus (SGCSE, discussed in Subheading 3.2.1.2.) has not been reported in primary GCSE.

3.1.1.2. Clonic Status Epilepticus

This is a rare condition usually seen only in infants and children. The EEG patterns are variable, showing rhythmic bilateral bursts of high-amplitude delta activity with intermixed spikes or polyspikes *(3)*. The bursts of spikes and polyspikes occur synchronously with clonic jerking.

3.1.1.3. Tonic Status Epilepticus

Generalized tonic SE occurs predominantly in those with the triad of the Lennox-Gastaut syndrome (mental retardation, multiple seizure types, and slow-spike-and-wave activity on EEG). In clinically obvious cases, there are brief (10–15-s) tonic contractions of the face, thorax, abdomen, and/or extremities. EEG may be necessary to make the diagnosis of tonic SE, as tonic motor activity may be very subtle, showing only mild tonic contractions of paraspinal musculature or upward deviation of the eyes. The EEG during tonic seizures shows generalized electrodecremental activity (voltage suppression) or brief runs of low-voltage generalized fast activity (GPFA; Fig. 3A). The amplitude of the ictal discharge gradually increases and the frequency decreases, sometimes followed by rhythmic generalized spikes *(11)*. Tonic seizures usually last less than 10 s, but can recur hundreds of times in a single night (Fig. 3B). Treatment with benzodiazepines has been reported to precipitate or worsen tonic SE in some cases *(13)*.

3.1.1.4. Myoclonic Status Epilepticus

Myoclonic SE is seen predominantly in two settings: with a history of myoclonic epilepsy and following a hypoxic-ischemic brain injury *(14)*. In myoclonic seizures, a generalized, frontally maximal irregular spike-and-wave or polyspike-and-wave

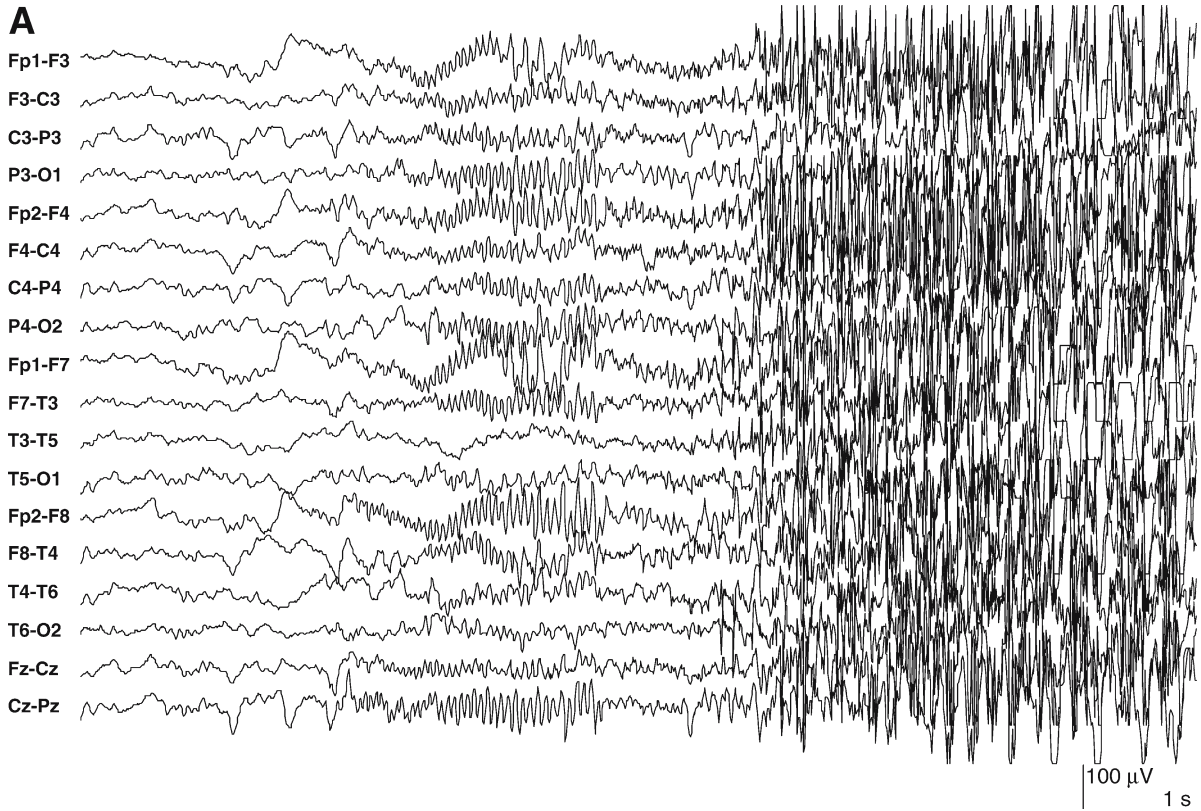
A
Fp1-F3
F3-C3
C3-P3
P3-O1
Fp2-F4
F4-C4
C4-P4
P4-O2
Fp1-F7
F7-T3
T3-T5
T5-O1
Fp2-F8
F8-T4
T4-T6
T6-O2
Fz-Cz
Cz-Pz
100 μV
1 s

Fig. 2.

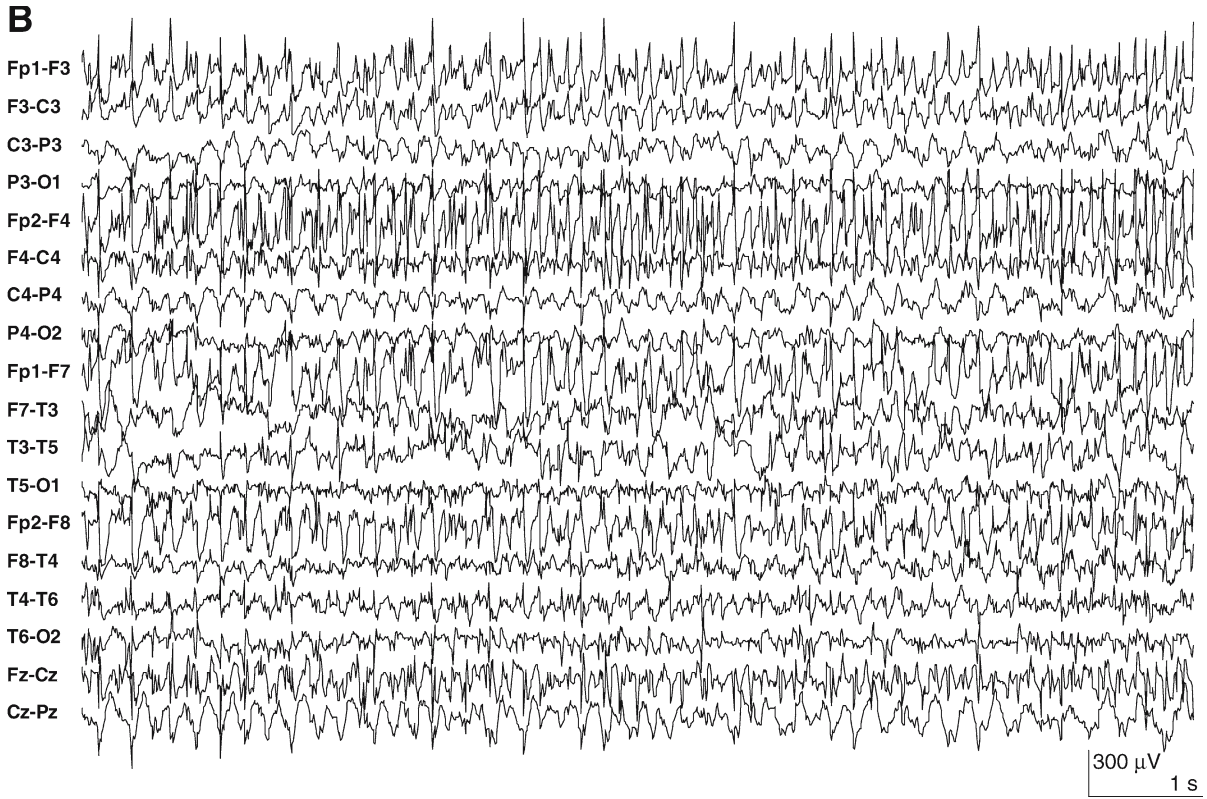

Fig. 2. A generalized tonic-clonic seizure (GTCS) in a 20-yr-old woman with cryptogenic generalized epilepsy. Typical seizures occurred twice a month, frequently as GCSE. **(A)** One seizure in primary GCSE begins with low-voltage diffuse beta activity, followed by diffuse muscle artifact as diffuse tremors begin. Note diffuse background slowing and attenuation prior to seizure onset. **(B)** The seizure continues with generalized high-voltage spike and slow-wave discharges at 5–6 Hz, correlating with clonic jerking of the extremities. The seizure lasted for 30 min before it was terminated by intravenous lorazepam and phenytoin.

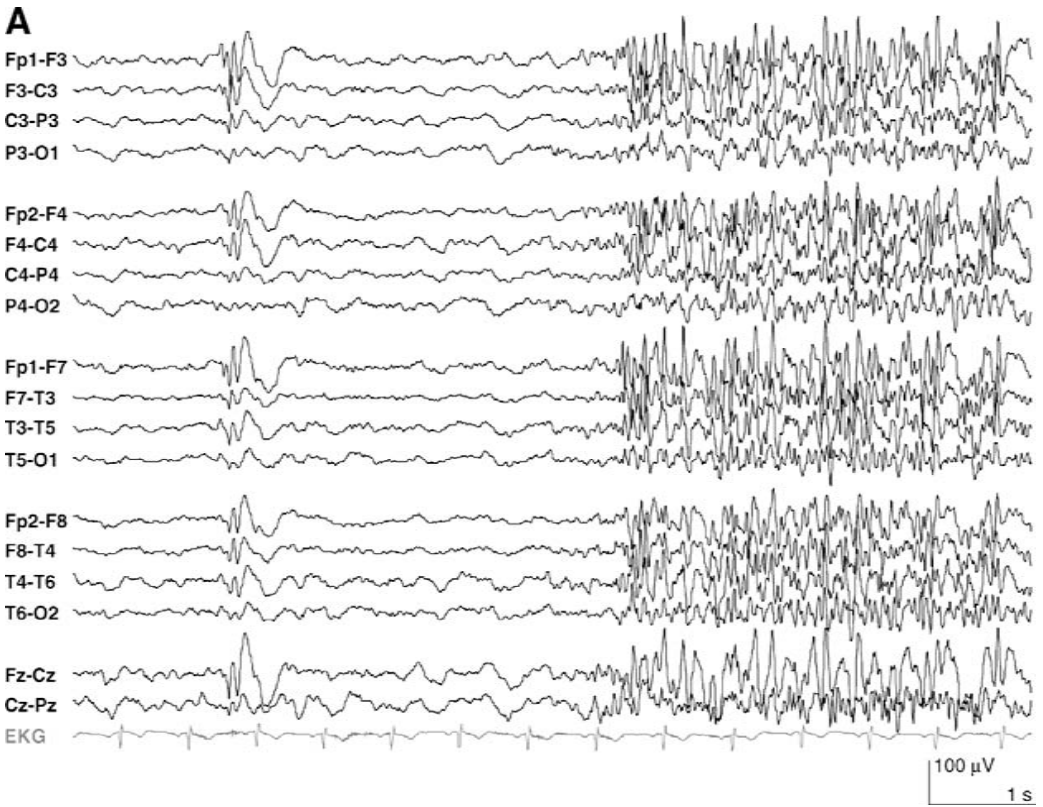
A
Fp1-F3
F3-C3
C3-P3
P3-O1
Fp2-F4
F4-C4
C4-P4
P4-O2
Fp1-F7
F7-T3
T3-T5
T5-O1
Fp2-F8
F8-T4
T4-T6
T6-O2
Fz-Cz
Cz-Pz
EKG
100 µV
1 s

Fig. 3.

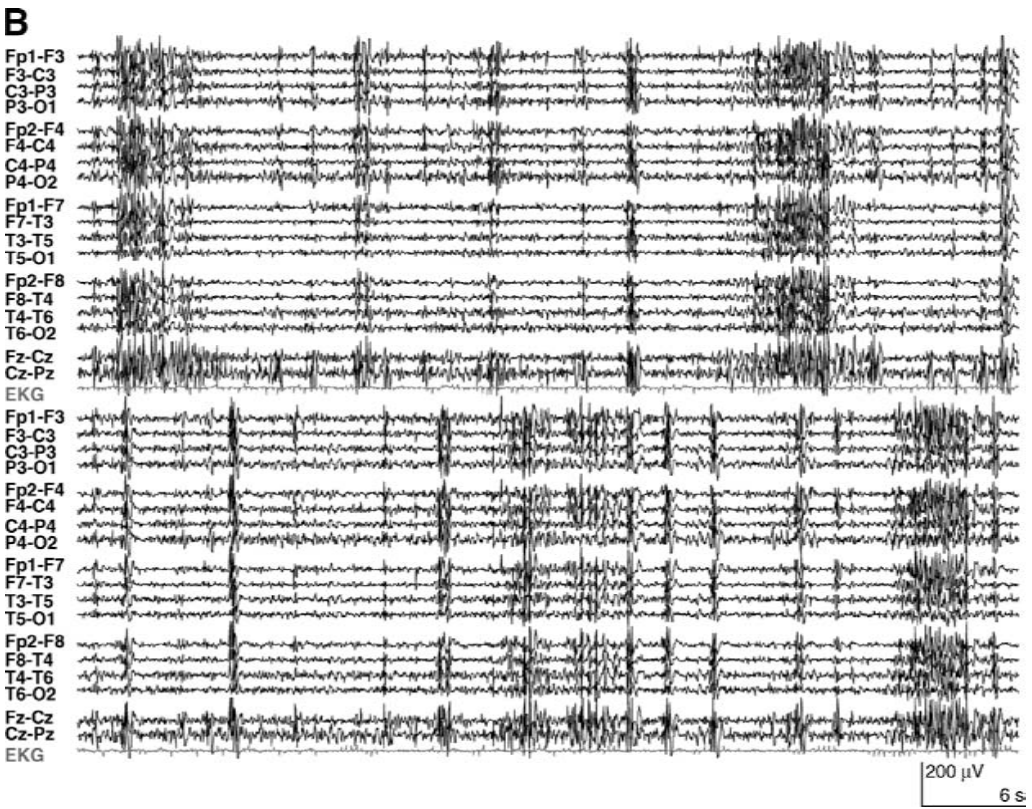

Fig. 3. Generalized tonic SE in a 24-yr-old woman with Down syndrome and Lennox-Gastaut syndrome. She was stuporous with frequent tonic extension of the arms and upward eye deviation. **(A)** Diffuse, frontally maximal, high-voltage semirhythmic beta activity during a tonic seizure. Background shows diffuse slowing and voltage attenuation. **(B)** Two minutes of EEG showing frequent brief tonic seizures, some with minimal clinical correlate.

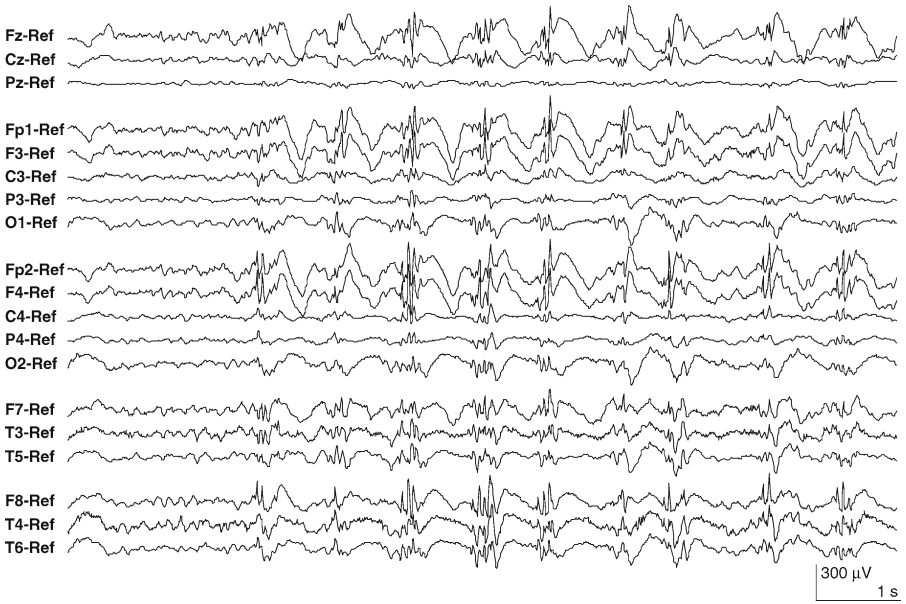

Fig. 4. Myoclonic SE in a 15-yr-old girl with juvenile myoclonic epilepsy. Shortly after awakening from sleep, she had a 2-h cluster of generalized, irregular myoclonic jerks of her arms and occasionally legs. Her mental status during the episode was normal. EEG shows frequent bursts of irregular generalized polyspike-and-wave activity, often in runs at 1 Hz.

pattern correlates with a clinical myoclonic jerk. These usually occur singly or in brief clusters soon after awakening. Some patients with primary generalized epilepsy may have prolonged and repetitive myoclonic seizures, with normal consciousness between individual myoclonic jerks *(15)*. In myoclonic SE, the EEG shows intermittent 1–2 s bursts of ictal discharges with intervening normal background EEG (Fig. 4). The ictal discharges are bilaterally symmetric. Myoclonic SE may also be seen in individuals with symptomatic generalized epilepsies such as Lennox-Gastaut syndrome. The EEG shows similar irregular spike-and-wave or polyspike-and-wave discharges, but with prominent intervening frontally maximal delta activity. Myoclonic SE in both primary and secondarily generalized epilepsies usually responds well to AED treatment *(14)*.

Myoclonic SE may also be seen in acute or chronic postanoxic myoclonus, usually following cardiac arrest *(16)*. Acute postanoxic myoclonus usually begins 8 to 24 h after a hypoxic insult *(17)*, with continuous irregular generalized or fragmentary myoclonic jerks. The background EEG shows severe voltage attenuation or a burst-suppression pattern, with superimposed generalized periodic epileptiform discharges (spikes or polyspikes) at a rate of 1 to 1.5 Hz (Fig. 5). Acute postanoxic myoclonic SE is associated with poor outcome and may be extremely refractory to therapy *(14,18,19)*. Aggressive therapy is probably not warranted, as myoclonic SE

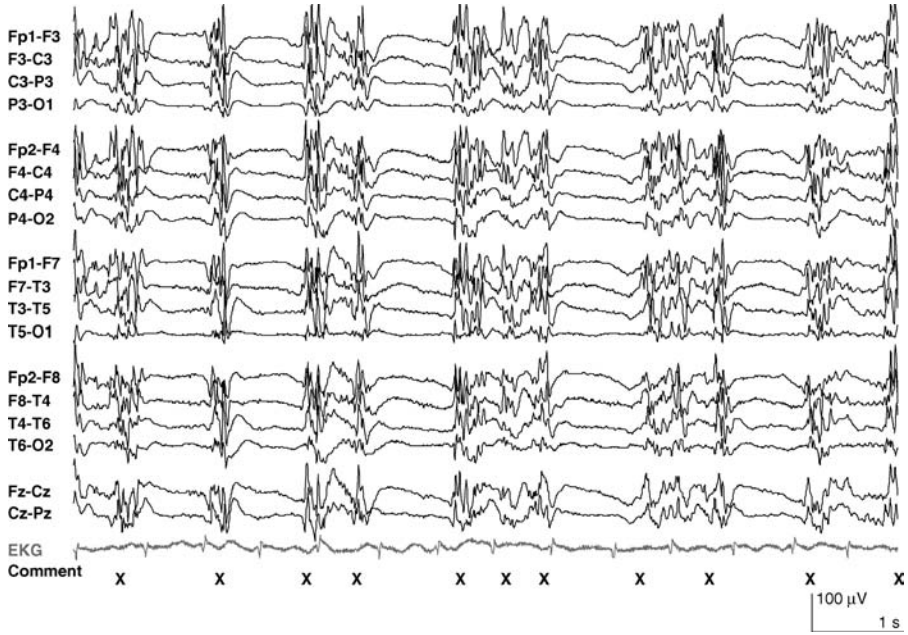

Fig. 5. Postanoxic myoclonic SE. Bursts of irregular high-voltage polyspike and polyspike-and-wave activity are followed by severe diffuse background attenuation. The X's indicate myoclonic jerks noted by the EEG technologist.

is usually a symptom of a severe anoxic insult, rather than a contributing factor to injury. Postanoxic myoclonic SE may be abolished by AEDs without improvement in neurologic outcome. Chronic postanoxic myoclonus (Lance-Adams postanoxic action myoclonus) *(20)* shows a variety of EEG patterns. Most often, irregular centrally maximal polyspike-and-wave discharges cause clinical segmental or generalized myoclonic jerks. The myoclonus is typically precipitated by action or stimulation.

3.1.2. Partial Onset

3.1.2.1. Secondarily Generalized Convulsive Status Epilepticus

Secondary GCSE accounts for 70 to 80% of GCSE and has high potential for morbidity and mortality. Seizures begin focally as simple or complex partial seizures (*see* Section 3.2.2.) but progress to generalized convulsions *(12)*. Treiman and colleagues proposed a progressive sequence of EEG changes during GCSE, based on recordings from animals and humans during various stages of SE *(6)*. Seizures initially are discrete (Fig. 6) and are followed by background slowing and attenuation until the next seizure begins. Next, seizures merge gradually, with waxing and waning of amplitude and frequency, and eventually become continuous (Fig. 7A). Continuous ictal discharges are frequently asymmetric, reflecting the

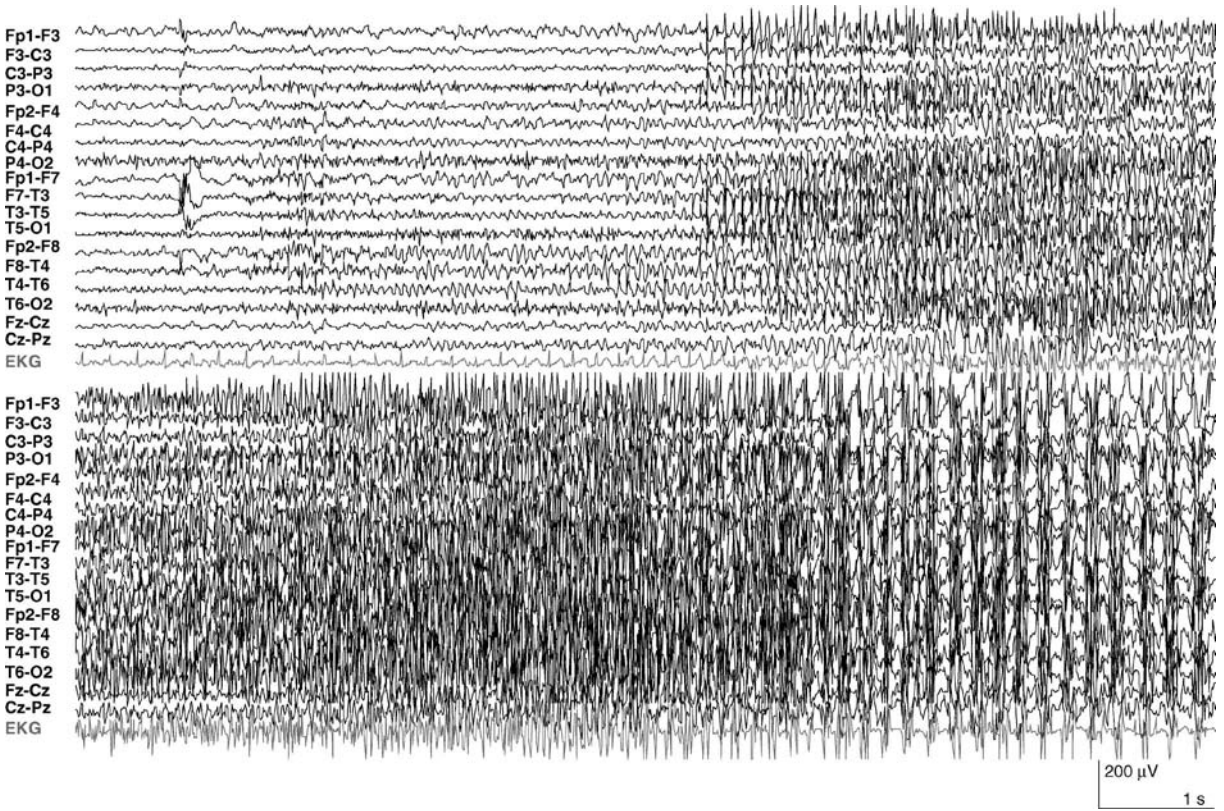

Fig. 6. A secondarily generalized tonic-clonic seizure in GCSE begins from the right temporal region with rhythmic theta activity. The seizure then spreads diffusely with rhythmic theta-alpha activity with superimposed muscle artifact, and develops into rhythmic bursts of polyspike-and-wave activity correlating to clonic jerks. Three similar prolonged seizures occurred over 40 min without return to normal consciousness.

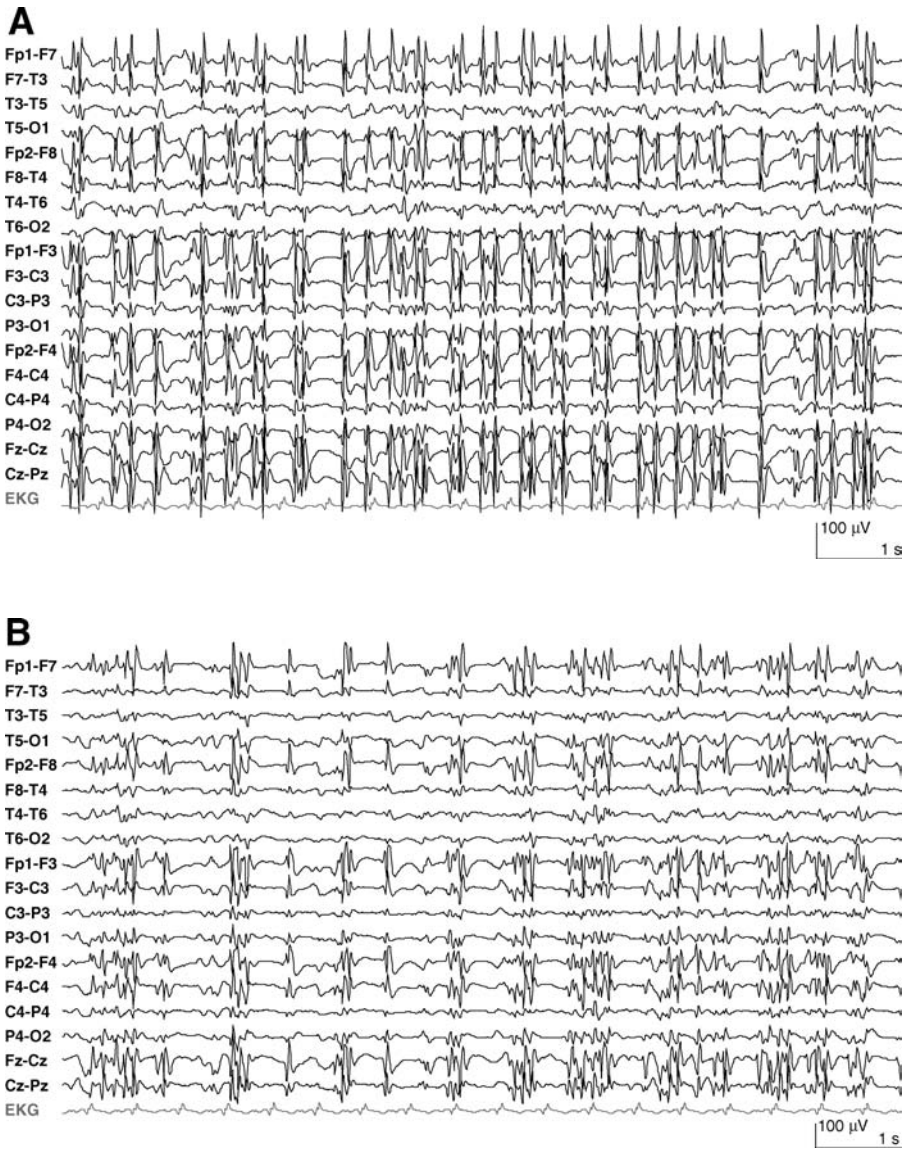

Fig. 7. Progressive EEG changes in subtle generalized convulsive SE (SGCSE). This 68-yr-old man with renal failure was comatose following treatment for GCSE with lorazepam, phenytoin, and phenobarbital. Exam showed nystagmoid eye movements and fine twitching of fingers. **(A)** Initial EEG revealed continuous generalized spikes and polyspikes. **(B)** After initiation of propofol, the EEG showed a discontinuous pattern of polyspikes followed by diffuse background attenuation. **(C)** Increase in propofol dose resulted in generalized periodic epileptiform discharges (PEDs or GPEDs) and cessation of myoclonic jerking. The epileptiform discharges are maximal in the frontal regions.

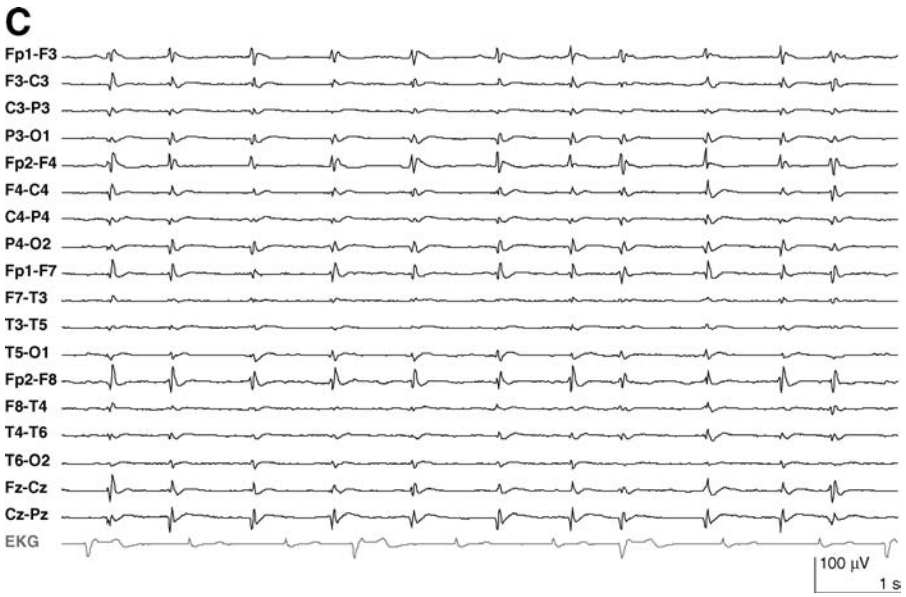

Fig. 7. *(Continued)*

partial onset of the seizures. As SE progresses, seizures become discontinuous, with brief (0.5–8 s) periods of generalized voltage attenuation or flattening (Fig. 7B). In late SE, bilateral repetitive periodic epileptiform discharges (PEDs) arise from a relatively flat background (Fig. 7C). As EEG becomes more discontinuous, clinical manifestations become more subtle, with subtle twitching of the limbs, nystagmoid eye movements, or even absence of motor movements.

Other investigators have failed to find the sequence of EEG changes proposed by Treiman *(21–23)*. While these EEG patterns were seen frequently, they often occurred out of sequence or in only some patients. Patients tended to persist in one EEG pattern throughout the course of SE. Controversy also exists about where SE ends and what effect treatment has on these patterns. Many electroencephalographers feel that PEDs are not an ictal pattern, as they can occur without any previous history of seizures (*see* Section 3.5.3.).

3.2. Nonconvulsive Status Epilepticus

3.2.1. Generalized Onset

3.2.1.1. Generalized Absence Status Epilepticus

3.2.1.1.1. Typical Absence Status Epilepticus. Typical absence status epilepticus (ASE) occurs both in individuals who have childhood-onset absence epilepsy and *de novo* in adults with no prior history of primary generalized epilepsy, often in the setting of AED withdrawal or toxic-metabolic encephalopathies. ASE is characterized by clouding of consciousness or a "twilight state," which may occur as

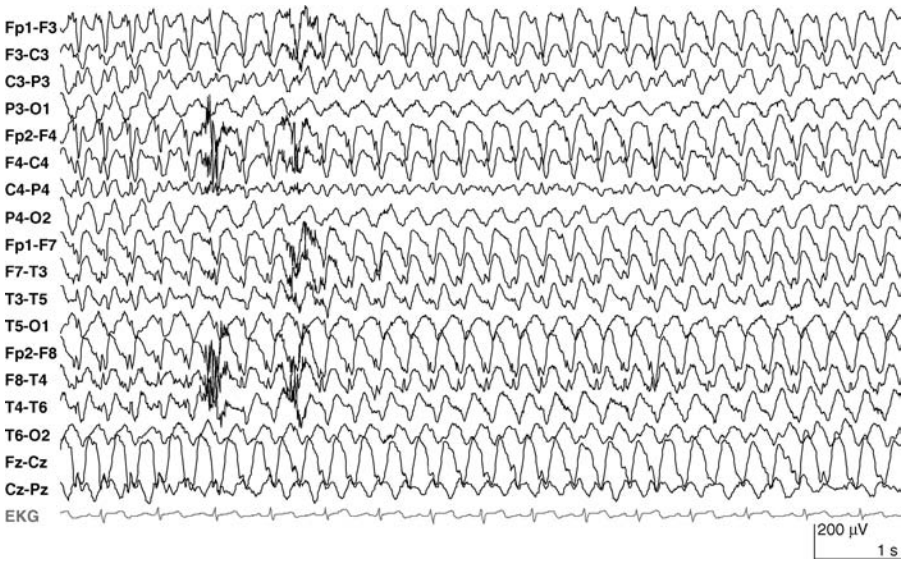

Fig. 8. Absence SE in a 42-yr-old woman with juvenile myoclonic epilepsy, now with confusion, slowed responses, and "pauses in speech." EEG shows a 3-Hz generalized spike-and-wave pattern.

individual seizures in rapid succession or, more commonly, as a single prolonged episode *(24)*. EEG, required for accurate diagnosis, shows generalized 3-Hz spike-and-wave discharges that occur as frequent repetitive seizures or as uninterrupted activity lasting for more than 30 min *(25,26)* (Fig. 8). Frontal and central head regions show the highest amplitude spike-and-wave discharges. Generalized poly-spike-and-wave discharges at 3 Hz may be seen in some cases. In patients without a history of absence epilepsy, the spike-and-wave component is often less prominent; Granner and Lee found stereotypic 3–3.5-Hz spike-and-wave activity in only 7% of patients *(5)*. Other EEG patterns include generalized rhythmic slowing with intermixed spike-and-slow-wave complexes (Fig. 9), irregular sharp-and-slow-wave discharges, or diffuse background slowing with superimposed bursts of fast activity *(24)*. The frequency of the spike-and-wave discharges decreases to less than 3 Hz and becomes irregular if ASE is prolonged *(12)*.

3.2.1.1.2. Atypical Absence Status Epilepticus. Atypical ASE occurs predominantly in patients with symptomatic generalized epilepsies such as Lennox-Gastaut syndrome *(3,11)*. EEG usually demonstrates bilateral spike-and-wave discharges with a frequency slower than 2.5 Hz (Fig. 10). These slow-spike-and-wave discharges are often irregular, may be asymmetric in distribution, and are frequently intermixed with generalized background slowing *(3)* (Fig. 11). Because patients often transition in and out of atypical ASE, electrographic seizures may not correlate exactly with clinical signs.

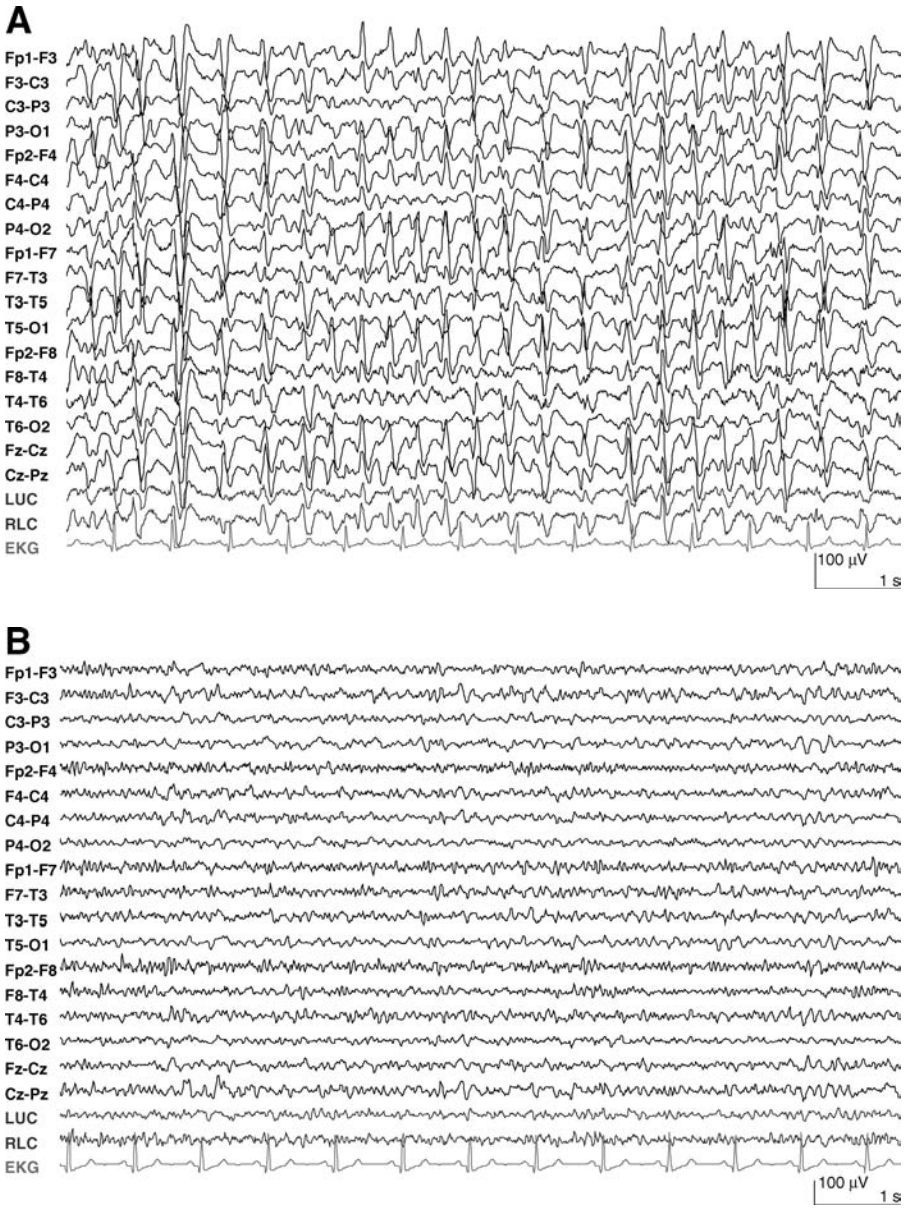

Fig. 9. Absence (generalized) SE in a 75-yr-old woman with a history of generalized tonic-clonic seizures, now confused and lethargic. **(A)** EEG shows rhythmic high-voltage 3-Hz sharp-and-slow-wave discharges, alternating with periods of diffuse delta activity and slower epileptiform discharges. **(B)** (same patient as A) EEG following administration of intravenous lorazepam shows complete cessation of ictal activity, with mild diffuse slowing and excess beta activity.

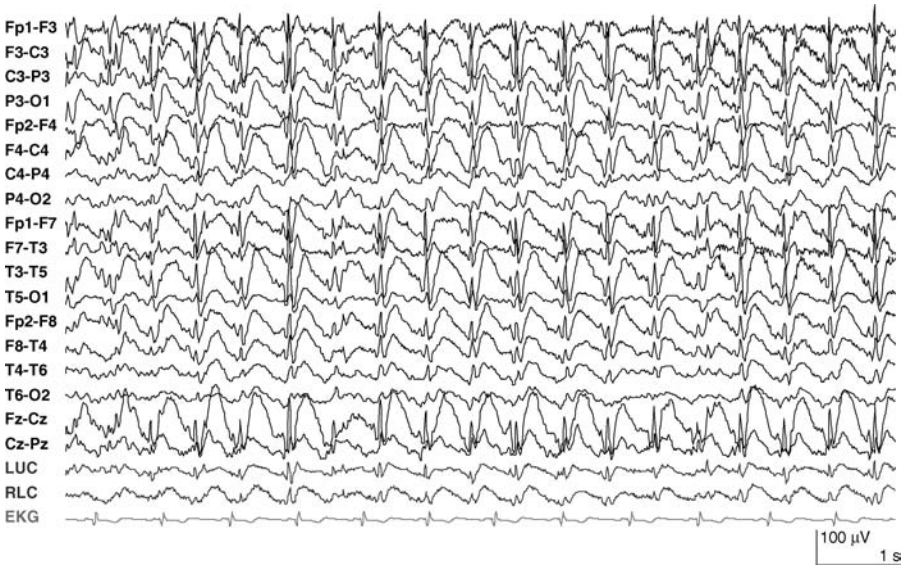

Fig. 10. Atypical absence status epilepticus in a 30-yr-old woman with mild mental retardation and intractable epilepsy, now with dizziness and slurred speech after being started on Dilantin. EEG shows generalized, frontally maximal slow-spike-and-wave discharges at 1.5 Hz.

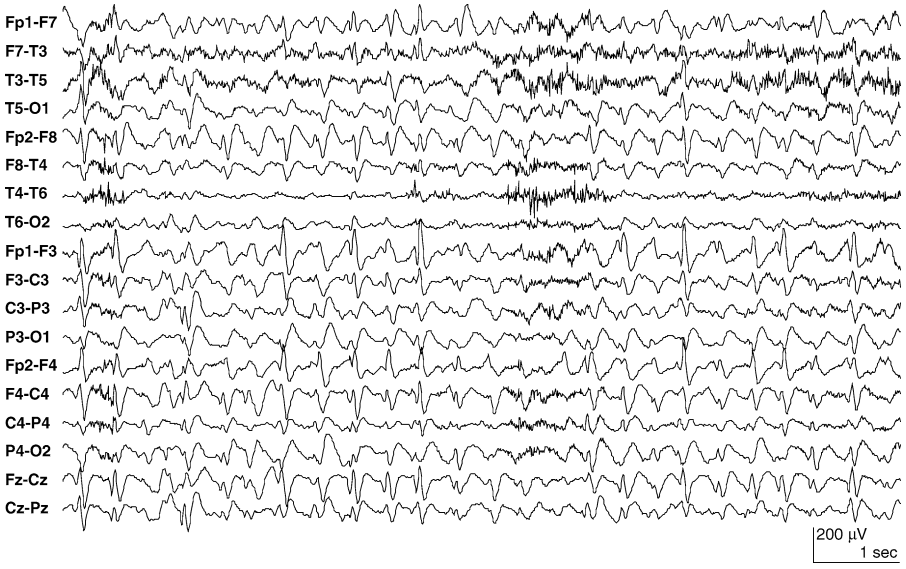

Fig. 11. Atypical absence SE in a 32-yr-old man with Lennox-Gastaut syndrome. He presented with prolonged staring episodes, between which he was lethargic. EEG during one of the episodes showed irregular 2–2.5-Hz generalized spike-and-wave discharges with intermixed rhythmic delta activity.

3.2.1.2. Subtle or Electrographic Generalized Convulsive Status Epilepticus

The term SGCSE describes the later stages of GCSE, usually in comatose patients with only minor or no motor manifestations (corresponding to Treiman's stages of discontinuous ictal activity and PEDs described in Section 3.1.2.1.) *(6,27)*. The EEG usually shows brief generalized bursts of polyspikes or generalized PEDs. This pattern is typically seen in patients with initially overt GCSE that gradually becomes subtle, as described above. When similar discharges are seen in patients with severe encephalopathy (e.g., uremia or postanoxic) but no history of seizures, they are less likely to represent an ictal pattern *(28)*. Abolition of electrographic seizures may not be accompanied by an improvement in clinical mental status. Such patients have high morbidity and mortality *(6,8,23,29)*.

3.2.2. Partial Onset

3.2.2.1. Simple Partial Status Epilepticus

Patients with simple partial status epilepticus (SPSE) present with ictal symptoms reflecting involvement of discrete regions of the brain, such as motor, sensory, special sensory, psychic, or autonomic symptoms, without impairment of consciousness *(30)*. Surface EEG has limited sensitivity for detection of ictal discharges that involve a small volume of brain tissue, so EEG in SPSE may be normal or show only patterns related to change in level of arousal or movement artifacts *(31)*. Between 20 and 35% of simple partial seizures may show an ictal correlate on surface EEG *(32)*. Focal fast frequency discharges, rhythmic waveforms with evolving morphology (Fig. 12), repetitive epileptiform discharges, or regional or lateralized alterations in EEG background activities may be seen *(31–33)*.

3.2.2.1.1. Epilepsia Partialis Continua. Epilepsia partialis continua (EPC) is a subtype of SPSE characterized by continuous motor seizures, usually irregular clonic muscle twitching, involving part or all of one side of the body. The relationship between clinical manifestations and EEG changes is inconsistent, and EEG may be completely normal in up to 10% of cases. One series reported focal discharges in only 22% of patients *(34)*, but use of additional scalp-electrodes can show focal discharges in up to 71% *(35)*. Back-averaging of EEG time-locked to clinical myoclonus may demonstrate a relationship between scalp recorded discharges and muscle jerks in 37 to 45% of patients *(34,35*). Epileptiform discharges in EPC are usually irregular spikes and sharp waves (Fig. 13). Periodic lateralized epileptiform discharges (PLEDs) can be seen in 8 to 14% of cases *(35,36)*. Although PLEDs are usually not considered an ictal pattern, when they are associated with a clinical correlate a diagnosis of partial SE is reasonable *(37)*. When underlying focal structural abnormalities such as Rasmussen's encephalitis or tumors are present, there may be underlying focal slowing and attenuation.

3.2.2.2. Complex Partial Status Epilepticus

Complex partial status epilepticus (CPSE) may begin with simple partial clinical features that progress to loss of consciousness, or consciousness may

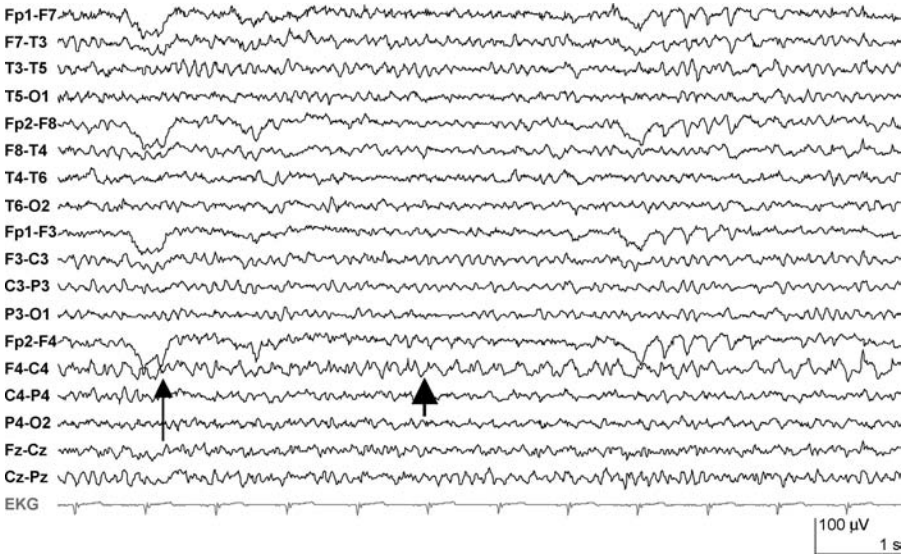

Fig. 12. Simple partial SE in a 48-yr-old woman with tuberous sclerosis who presented with nearly continuous focal motor seizures affecting the left face and oropharynx. EEG during many of the seizures showed no electrographic correlate. During this seizure, low-voltage semirhythmic theta activity is seen at F4-C4 (arrow), evolving into rhythmic delta activity (arrowhead). Seizures occurred every 2 to 3 min, often precipitated by speech or other mouth movements, and eventually required intubation for airway protection.

be impaired at onset. The extensive variety of clinical presentations of CPSE makes EEG necessary for diagnosis in most cases. In contrast to SPSE, nearly all complex partial seizures (CPS) show discernible surface EEG changes, with the exception of brief frontal or parietal lobe seizures *(38,39)*. A sequence of EEG patterns similar to that in GCSE may be seen. Focal onset is followed by evolution in distribution, amplitude and frequency, according to commonly accepted criteria for detecting electrographic seizures *(38,40,41)*. Interictal slowing and attenuation are seen between discrete seizures, which gradually merge to produce continuous focal seizure activity. Periods of intermittent flattening and periodic epileptiform discharges may develop as SE continues *(42)*.

Ictal patterns in CPSE include repetitive epileptiform discharges, rhythmic low voltage fast activity, and slower rhythmic frequencies in the theta and delta range. The wide range of EEG patterns reflects differences in location of ictal onsets and propagation of seizures *(43)*. CPSE may arise from any brain region, although extratemporal onsets may be more common *(44)*. Fast-frequency discharges may be present when seizures originate from neocortical regions near surface electrodes, while deeper foci tend to produce slower frequency patterns. As CPSE progresses, the ictal discharges increase in amplitude, slow in frequency, and broaden in distribution. CPSE may be characterized by either repetitive complex partial seizures

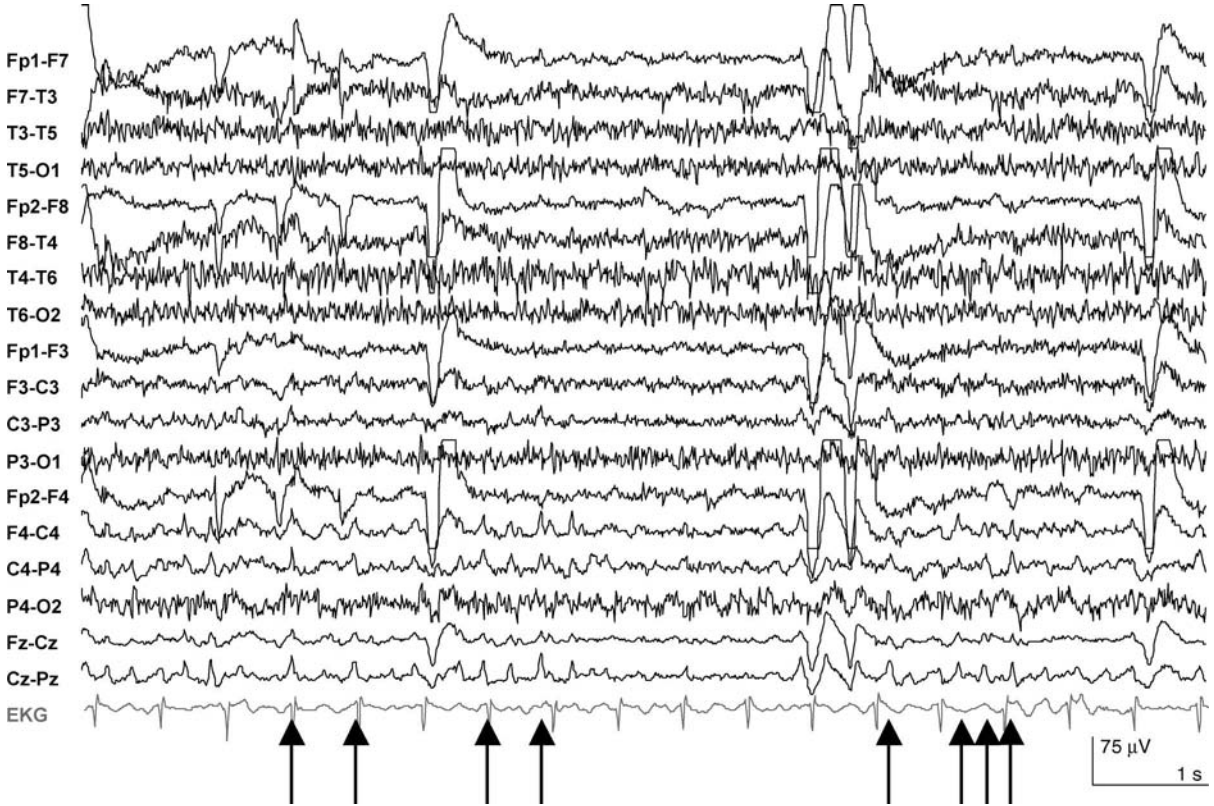

Fig. 13. Epilepsia partialis continua (EPC) in a 20-yr-old woman with right parietal cortical dysplasia. She presented with a 2-mo history of continuous irregular jerking of the left fingers and hand, with painful dystonic posturing of the left hand and elbow. EEG shows low-voltage semi-rhythmic sharp waves in the right central-parietal region (F4-C4 and C4-P4) and at the vertex (Cz-Pz).

with background slowing between seizures (Fig. 14) or continuous ictal rhythms (Fig. 15), corresponding to cycling or continuous clinical manifestations *(3,45–47)*. Rarely, ictal patterns may arise independently from both hemispheres (Fig. 16). Frequently, patients with localization-related epilepsy and SE show continuous diffuse spike-and-wave EEGs, resembling those of ASE *(5,48,49)*.

The EEG patterns of seizures in CPSE are similar to those seen in isolated CPS. The EEG changes may remain focal throughout the course of the SE episode *(32)*. CPS arising from mesial temporal regions usually begin with unilateral temporal 5–7-Hz rhythmic activity that appears within 30 seconds of the initial clinical symptoms or signs *(40)*. Interictally, there is focal slowing or attenuation on the side of seizure onset. In neocortical temporal lobe epilepsy, ictal discharges are more widely distributed, often over the entire hemisphere. In general, neocortical temporal CPS begin with slower frequencies, show less stable frequency and voltage, and appear later after clinical signs than mesial temporal CPS *(41)*. Ictal EEG is nonlocalizing or normal in more than half of frontal lobe CPS *(38)*. Scalp electrodes may show no ictal correlate because the generator of ictal discharges is deep, or because muscle and movement artifact produced by prominent motor activity obscures the EEG. Focal rhythmic alpha or beta activity is sometimes seen at the onset of frontal CPS originating near scalp electrodes *(38)*. In most patients with frontal CPSE, scalp EEGs eventually show bilateral sharp-and-slow-wave activity *(44)*. Similarly, scalp EEG is usually nonlocalizing or falsely localizing in parietal CPS *(39)*. No changes may be seen on scalp EEG until the seizure spreads to mesial temporal structures, producing ictal patterns typical of mesial temporal CPS.

3.2.2.3. Electrographic Partial Status Epilepticus

Electrographic partial SE is seen in stuporous or comatose patients with no clear clinical signs of seizure activity *(43)*. Seizures may be either continuous or repetitive, and EEG patterns are similar to those in SPSE and CPSE. Such partial SE is frequently seen after strokes or other acute brain injuries, and should be suspected when patients do not stabilize or improve as expected *(33)*.

3.3. Age-Related Status Epilepticus

3.3.1. Neonatal Status Epilepticus

Continuous EEG monitoring is essential in the routine detection and treatment of neonatal seizures *(50)*; many neonatal seizures may have few or no clinical manifestations and may be missed if EEG is not utilized *(51)* (*see* also Chapter 17). Electrographic seizures without clinical accompaniment are most commonly seen in neonates with severe brain injury *(52)*, following treatment with AEDs *(53)*, and in pharmacologically paralyzed infants. Equally important, not all repetitive neonatal movements are epileptic. Abnormal movements such as swimming, pedaling, rowing, myoclonic jerks, jitteriness, and stimulus-sensitive clonus may be misinterpreted as seizures if concurrent EEG monitoring is not available, sometimes resulting in inappropriately aggressive treatment.

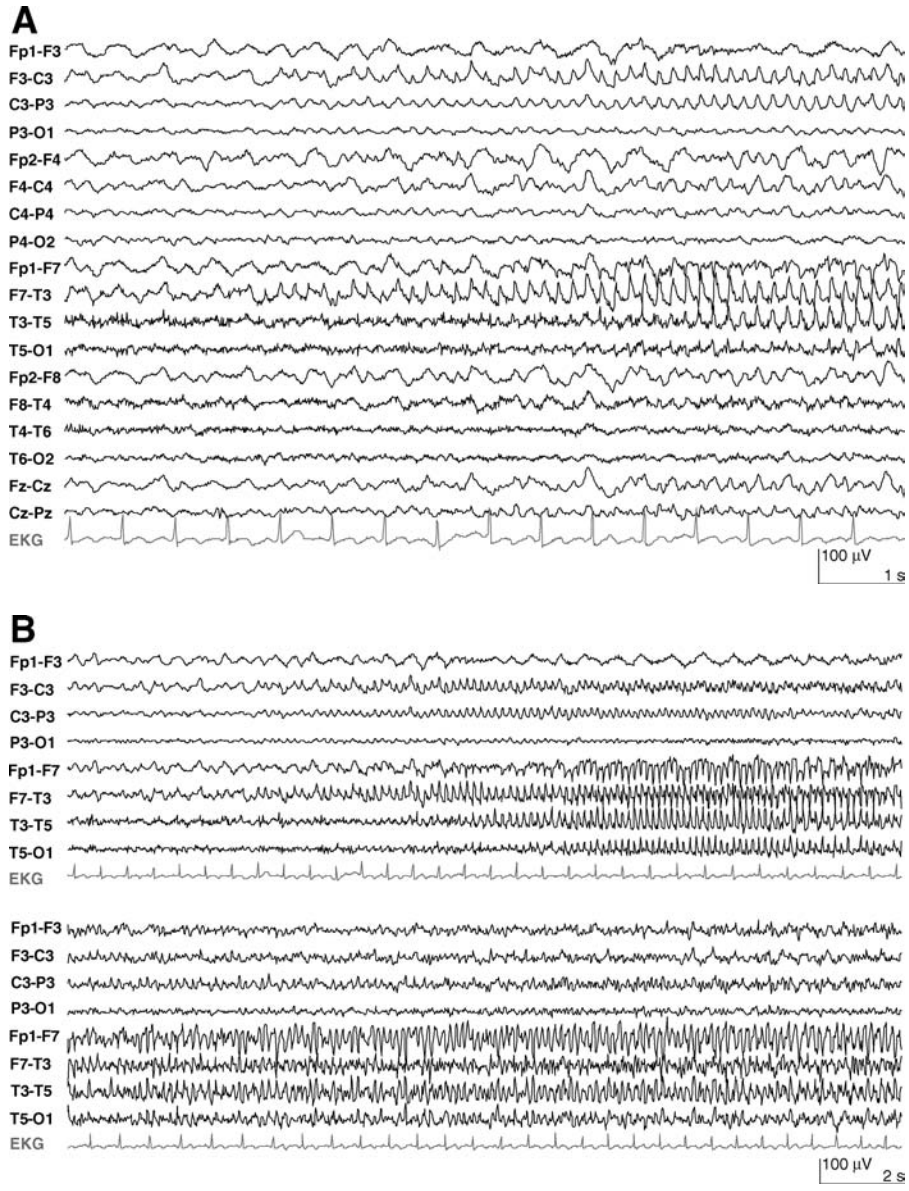

Fig. 14. Complex partial SE in a 21-yr-old right-handed man with intractable temporal lobe epilepsy. This seizure occurred in a cluster of seven seizures over a 3-h period, with persistent confusion and severe aphasia between seizures. **(A)** Onset with rhythmic sharp theta activity in the left anterior temporal region. **(B)** Continuation of the same seizure, with spread to involve the entire left temporal region and later the central parasagittal region. The amplitude of the theta activity increases and the frequency slows as the seizure progresses. The seizure remained localized to the left hemisphere for 5 min, then ended. Clinically, the patient was unresponsive, with quiet staring and oral automatisms.

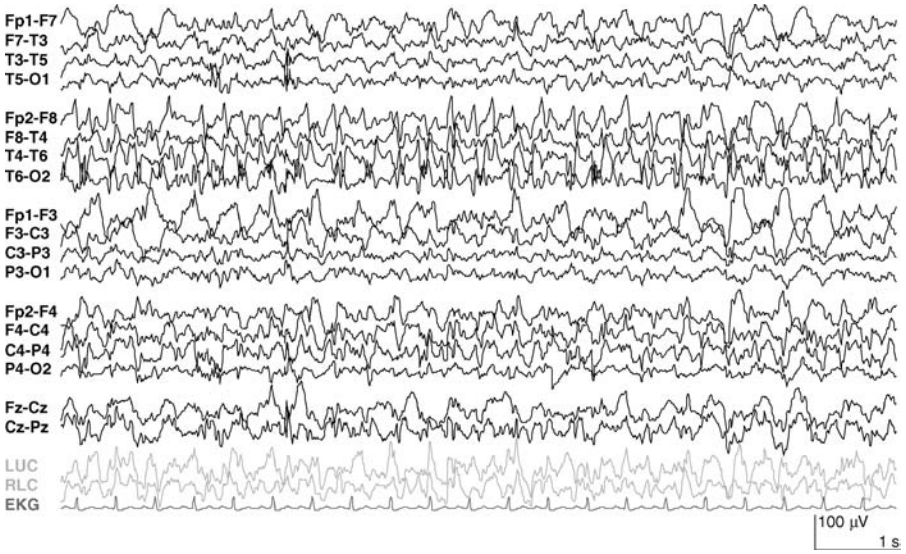

Fig. 15. Complex partial SE in a 46-yr-old man with central nervous system vasculitis. He presented with diffuse tremulousness and perseveration for 4 h. EEG showed continuous right temporal ictal activity.

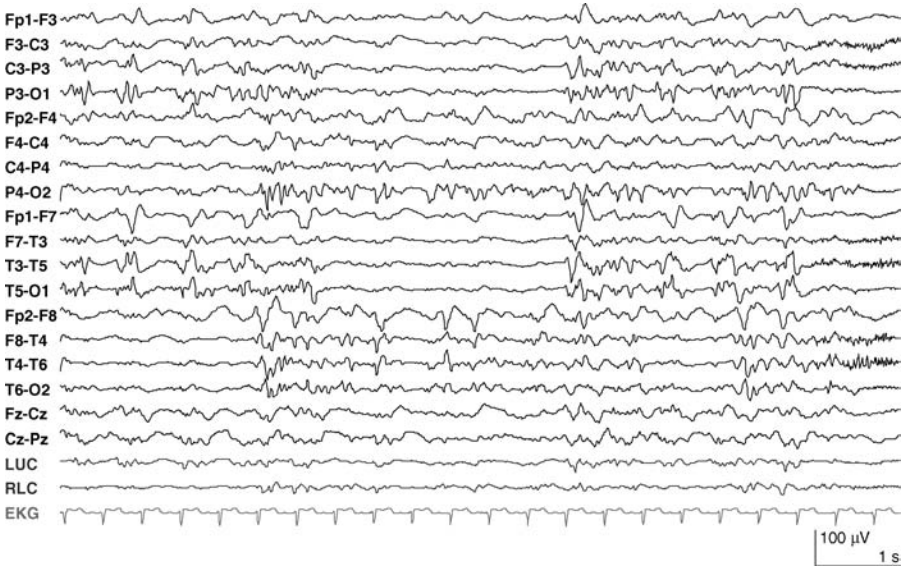

Fig. 16. A 68-yr-old woman with herpes encephalitis and SE. At the time of this EEG, she was comatose. EEG shows discontinuous ictal activity independently from the right and left hemispheres. The seizures were refractory to treatment with intravenous midazolam and propofol.

Electrographic patterns of neonatal seizures differ from those of older patients, likely secondary to incomplete myelination and neuronal migration. Ictal discharges are nearly always focal and may be localized to relatively small brain regions *(54)*. Multifocal seizures are commonly seen with multifocal or diffuse brain injury. Frequencies are most often in the alpha, theta, or delta range, but the frequency and morphology may vary within a single seizure and from seizure to seizure. Alpha-frequency discharges tend to be low voltage, while slower-frequency (theta and delta) seizures may show higher amplitude. As opposed to adult seizures, neonatal seizures tend to remain localized to one brain region and may show little or no evolution in amplitude, frequency, or morphology *(54)* (Fig. 17).

3.3.2. Electrical Status Epilepticus During Slow Sleep or Continuous Spikes and Waves During Sleep

Electrical status epilepticus during slow sleep or continuous spikes and waves during sleep (ESES), first described by Patry and colleagues *(55)*, begins in childhood and is characterized by seizures, continuous generalized spike-and-wave discharges during slow-wave sleep, and progressive cognitive decline. Rare focal or occasionally generalized epileptiform discharges are seen in the waking EEG. During deep stages of non-rapid eye movement (NREM) sleep, continuous generalized or bilaterally synchronous spike-and-slow-wave complexes occupy at least 85% of slow sleep *(56,57)*, usually at a rate of 1.5 to 3.5 Hz (Fig. 18). The spike component is usually more prominent than the slow wave component. During rapid eye movement (REM) sleep, epileptiform discharges similar to the waking EEG are seen. This pattern usually disappears between the ages of 5 and 15 yr.

3.3.3. Landau-Kleffner Syndrome

Landau-Kleffner syndrome is characterized by an acquired aphasia, seizures, and a behavioral disorder *(58)*. The language disorder, initially an auditory agnosia with progressive decline, begins before age 7 in previously normal children. The waking EEG may be normal or show unilateral or bilateral temporal spike-and-wave discharges. During sleep, there are bursts of diffuse or multifocal spike-and-wave discharges. Focal spike-and-wave discharges are seen most commonly in the anterior and mid-temporal regions, but may also occur in the temporo-parieto-occipital regions *(57)* (Fig. 19). In contrast to ESES, epileptiform discharges are present in less than 85% of slow-wave sleep, and may occur during REM sleep *(59)*. The EEG manifestations usually appear between 3 and 5 yr and resolve after approx 15 yr of age.

3.4. Nonepileptic Status Epilepticus (Psychogenic or Pseudostatus Epilepticus)

Psychogenic status epilepticus can be difficult to diagnose definitively without EEG monitoring. Pseudostatus Epilepticus often does not respond to initial treatment for SE *(60)*, and even expert clinicians may be unable to distinguish

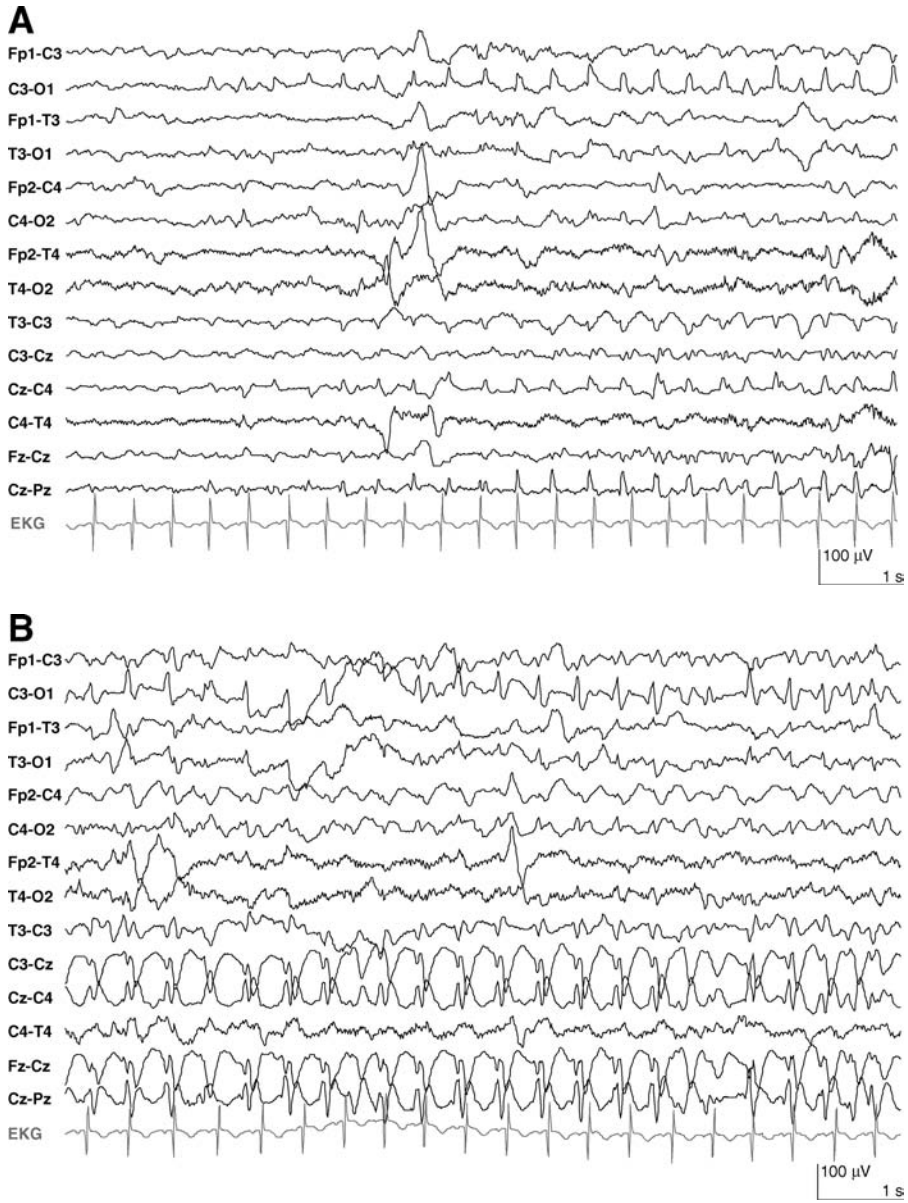

Fig. 17. Neonatal SE in a 32-wk conceptional age neonate with left periventricular hemorrhage. **(A)** EEG shows repetitive 2-Hz sharp waves arising from the left central parasagittal region (CZ, C3). The frequency of the ictal discharge is much lower than that usually seen in adult seizures. **(B)** Continuation of the same seizure, showing evolution into rhythmic sharp and slow-wave discharges over the vertex and left central parasagittal region. This seizure remained restricted to this region and did not show any change in frequency.

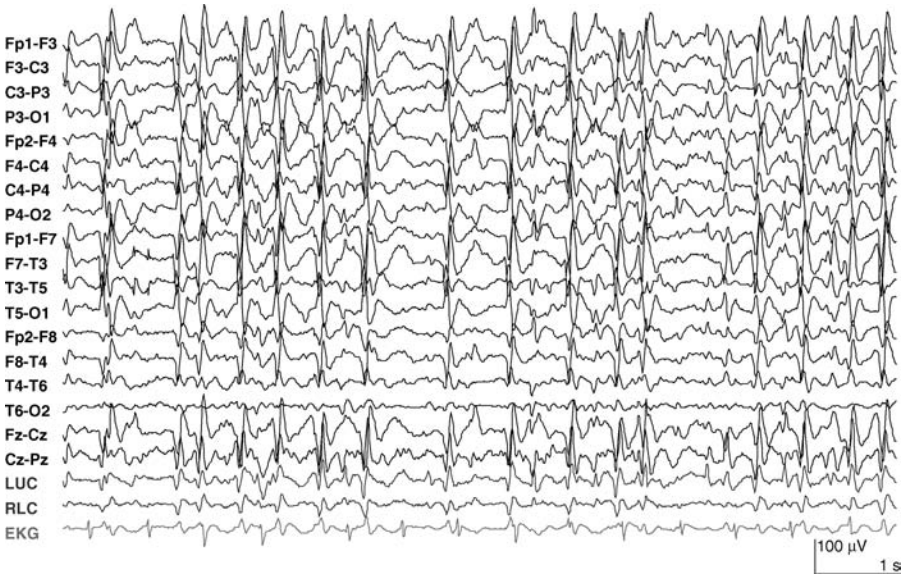

Fig. 18. Electrical status epilepticus in sleep (ESES) in a 12-yr-old girl. She presented with a single generalized tonic-clonic seizure and deterioration in school performance. EEG in sleep showed continuous high-voltage bilaterally symmetric sharp-and-slow-wave discharges at 1–3 Hz.

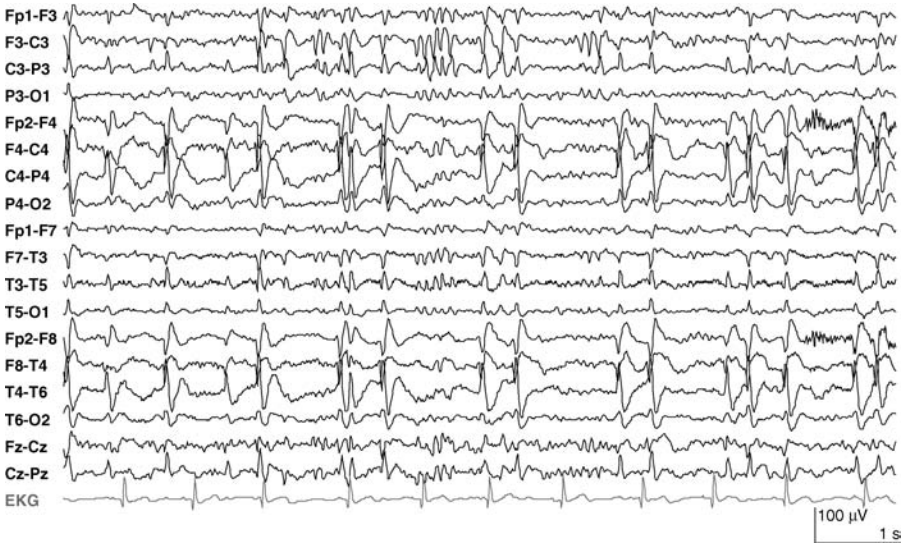

Fig. 19. Landau-Kleffner syndrome in a 4-yr-old boy with a history of language regression. EEG shows high voltage sharp-and-slow-wave discharges over the right centrotemporal region, with less prominent polyspikes over the left centrotemporal region.

prolonged psychogenic seizures from generalized or other types of SE. Incorrect diagnosis may lead to inappropriate use of general anesthesia and mechanical ventilation *(61,62)*. If clinical manifestations of SE are atypical and initial treatment fails, the diagnosis of SE should be confirmed by EEG prior to intubation and general anesthesia. Background activity is usually normal (Fig. 20A) in patients with pseudostatus mimicking NCSE (i.e., staring and unresponsiveness). Muscle and movement artifact may obscure the EEG in generalized pseudostatus epilepticus, but postictal slowing is the rule following GTCS. The presence of a normal alpha rhythm immediately following an apparent GTCS or during brief pauses in convulsive motor activity provides strong evidence for pseudostatus epilepticus (Fig. 20B).

Repetitive nonepileptic movements such as posturing, stretching, chewing, and blinking may raise the question of NCSE in obtunded or comatose patients. EEG monitoring may be necessary to rule out epileptic seizures. "Stimulus-responsive pseudoictal discharges" (SRPIDs), consisting of focal or generalized quasiictal or periodic discharges, have been described following stimulation or arousal in comatose patients *(63)*. These most likely represent abnormal arousals rather than ictal activity.

3.5. Controversial Patterns

Periodic patterns, commonly seen in confused, obtunded, or comatose patients, are controversial and have a variable relationship to clinical seizures. While most investigators have considered periodic epileptiform discharges (PEDs) to be post- or interictal phenomena *(64)*, others argue that PEDs are ictal patterns *(12)*. Some electroencephalographers would consider PEDs with a frequency greater than 2 Hz to be ictal, while others require associated clinical signs of seizures and improvement after treatment with AEDs. The following section provides examples of the most common periodic patterns and their relationship to status epilepticus.

3.5.1. Periodic Lateralized Epileptiform Discharges

Periodic lateralized epileptiform discharges (PLEDs) were first described by Chatrian and colleagues as repetitive lateralized polyphasic sharp-and-slow wave or spike-and-wave complexes, with repetition rates of 0.5 to 2 Hz *(36)*. The discharges are typically broadly distributed over most of one hemisphere and may reflect to the opposite hemisphere as well (Fig. 21A). Between PLEDs, background activity is severely attenuated and slow. Clinically, patients with PLEDs are usually obtunded, with focal neurologic signs and often focal motor seizures. PLEDs occur most commonly after acute large destructive lesions such as stroke and infection, but also in chronic seizure disorders and static lesions *(65)*. One series of 586 cases of PLEDs *(66)* found the etiology to be stroke in 35%, mass lesion in 26%, infection (mostly herpes simplex encephalitis) in 6%, anoxia in 2%, and other causes in 22%. PLEDs are usually transient, typically disappearing after a few days to weeks.

PLEDs are usually not considered an ictal pattern, but are highly associated with seizures. Clinical seizures occur in 75 to 84% of patients with PLEDs *(66,67)* and electrographic seizures in even higher proportions. The term "PLEDs plus" is used

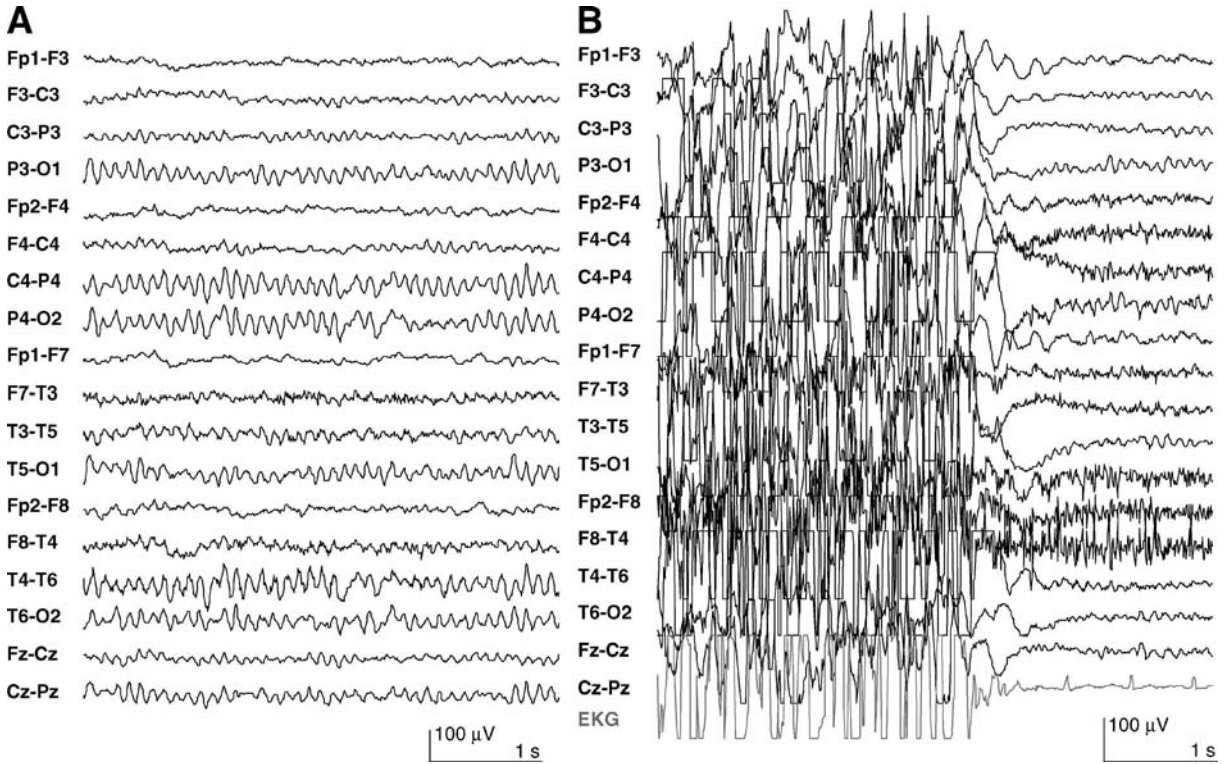

Fig. 20. Nonepileptic SE. **(A)** EEG of a 14-yr-old boy with epilepsy and multiple hospital admissions for nonconvulsive SE, characterized by staring, unresponsiveness, and eyelid fluttering for up to several hours. EEG during one typical 3-h event showed a normal alpha rhythm and posterior slow waves of youth. **(B)** EEG following more than 30 min of continuous generalized shaking of arms and legs (causing diffuse muscle artifact) shows normal background activity and posterior alpha rhythm, confirming a diagnosis of nonepileptic events. Similar normal alpha activity was seen during brief pauses in muscle artifact.

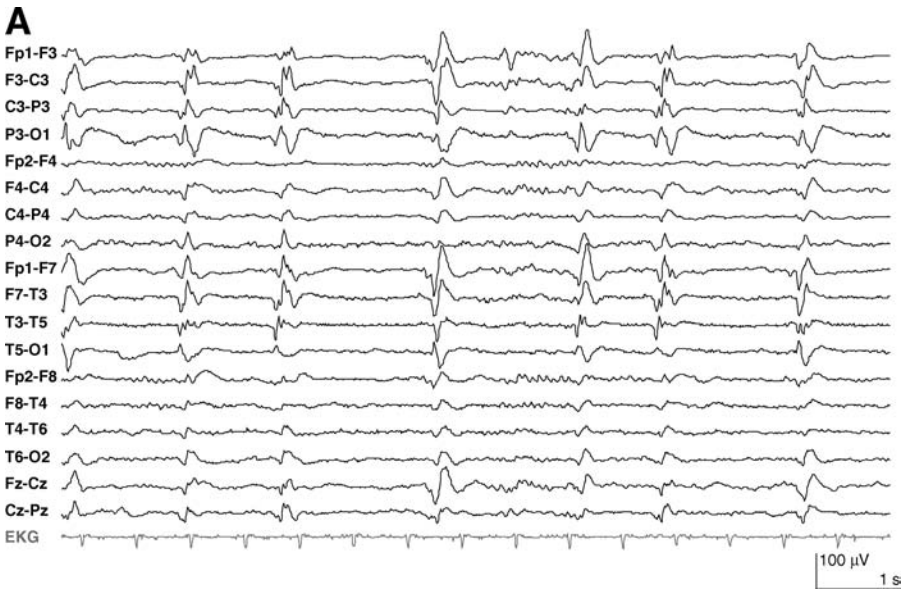

Fig. 21. Periodic lateralized epileptiform discharges (PLEDs) in a 68-yr-old woman with a left middle cerebral artery infarct. **(A)** PLEDs over the left hemisphere consist of polyphasic sharp waves with a broad field, maximal in the temporoparietal region, occurring at a rate of 0.5–1 Hz. There is some extension of the field to the right hemisphere as well. Background activity between the PLEDs is severely attenuated. **(B)** PLEDs plus, same patient. Several hours later, EEG revealed PLEDs followed by brief (1 s) bursts of beta and epileptiform activity. **(C)** PLEDs evolving into electrographic seizure, same patient. An electrographic seizure is seen arising from the left temporoparietal region. PLEDs are initially seen, but are gradually replaced by ictal activity involving most of the left hemisphere. This seizure had no clinical correlate.

to describe PLEDs with complex morphology, prolonged afterdischarges, intervening fast frequencies, and rapid (>2 Hz) repetition rates (Fig. 21B) *(32,68)*. PLEDs plus are highly associated with clinical seizures. Seizures typically begin with fast rhythmic activity, often with a field distinct from that of underlying PLEDs, and PLEDs then disappear (Fig. 21C). Less commonly, PLEDs themselves may be ictal, usually with a discharge frequency greater than 1.5 to 2 Hz. Clinical manifestations of PLEDs are typically epilepsia partialis continua, with repetitive irregular jerks of the contralateral face or extremities. Several studies have also found focal hyperperfusion on single photon-emission computed tomography (SPECT) *(69,70)* or positron emission tomography (PET) *(71)* during PLEDs, suggesting that PLEDs may be ictal in some cases. Patients with PLEDs plus or PLEDs with intermittent electrographic seizures should be treated more aggressively with AEDS.

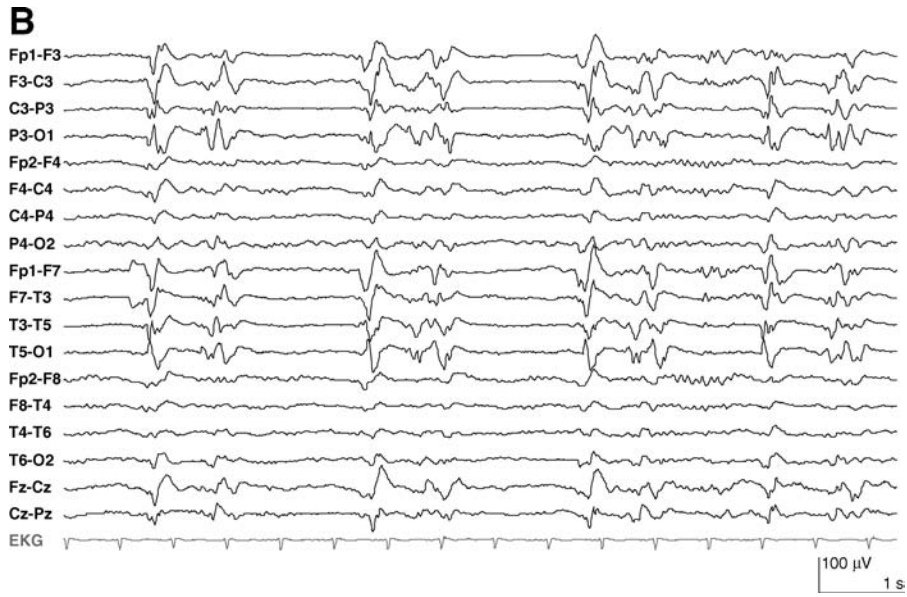

Fig. 21. *(Continued)*

3.5.2. Bilateral Independent Periodic Epileptiform Discharges

Bilateral independent periodic epileptiform discharges (BiPLEDs) are morphologically similar to PLEDs, but occur asynchronously and independently over the two hemispheres. Discharges over each hemisphere have different amplitudes, fields, and repetition rates (Fig. 22). Background activity is usually severely attenuated bilaterally. BiPLEDs are seen with acute bilateral destructive lesions such as anoxic encephalopathy and CNS infection *(72)*. BiPLEDs are associated with poorer mental status (coma in 72 vs 24%) and higher mortality rates (61 vs 29%) than PLEDs *(72)*, but focal seizures are less common (55 vs 80%).

3.5.3. Generalized Periodic Epileptiform Discharges

Generalized periodic epileptiform discharges (GPEDs) are continuous generalized sharp-and-slow waves, spikes, polyspikes, or triphasic waves often with a repetition rate of approx 1 Hz, arising from a diffusely attenuated background (Fig. 7C). These periodic discharges may be seen after severe anoxia or other metabolic insults, or in the late stages of GCSE. When due to anoxia, GPEDs are a poor prognostic sign, with death or severe neurologic sequelae in most patients *(16)*. Treiman and colleagues consider GPEDs to be ictal and recommend aggressive AED therapy *(73)*, while others believe that GPEDs are symptoms of severe acute neuronal injury rather than seizures, and do not require aggressive treatment *(64,74,75)*. One study of GPEDs did not find any features that could clearly distinguish between GPEDs after SE and GPEDs after anoxia *(28)*. GPEDs tend to persist even with aggressive

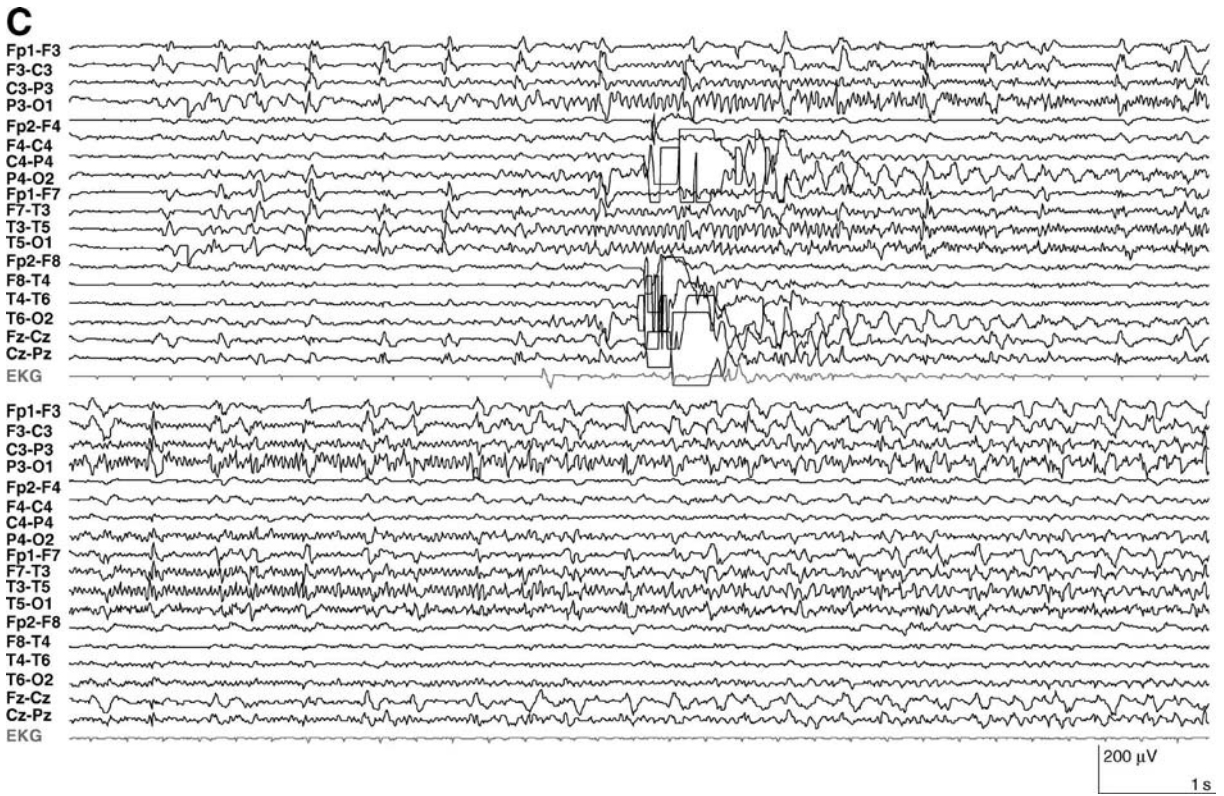

Fig. 21. *(Continued)*

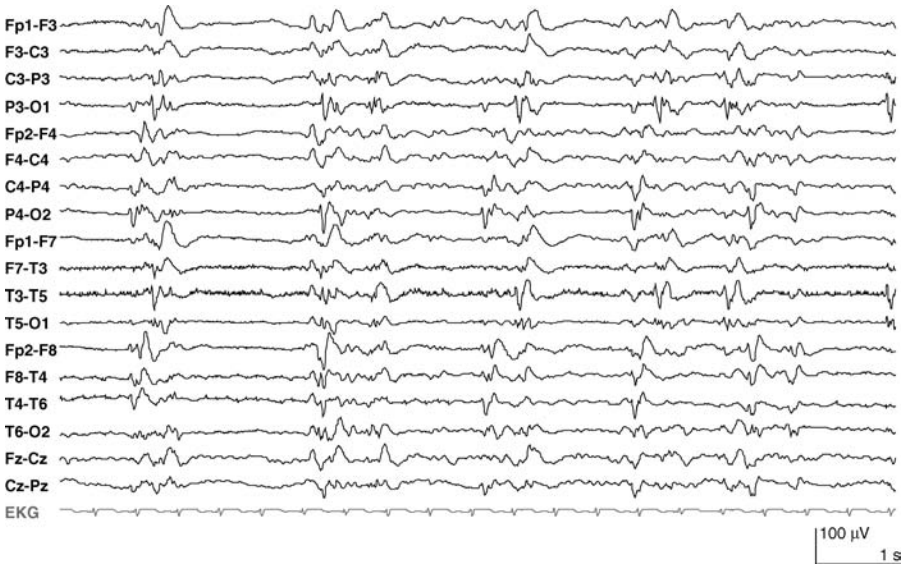

Fig. 22. Bilateral periodic epileptiform discharges (BiPLEDs) in a 68-yr-old woman with herpes encephalitis. PLEDs are seen arising independently from the left and right hemispheres.

therapy, and it is not known whether or not patients benefit from treatment of these EEG findings.

3.5.4. Triphasic Waves

Triphasic waves are named for their multiphasic morphology, with an initial low-amplitude, negative sharp wave followed by a high-amplitude positive sharp wave and a lower amplitude, negative broad slow wave (Fig. 23). They are broadly distributed, usually with maximal amplitude in frontal regions, but may also be maximal posteriorly. An anterior-to-posterior or posterior-to-anterior time lag may be present (Fig. 23). Triphasic waves frequently occur in clusters or continuously at 0.5 to 2 Hz *(10)*. They may increase with stimulation and attenuate with deeper levels of obtundation or coma. Triphasic waves occur in metabolic encephalopathies, most commonly hepatic encephalopathy, as well as uremia, hypothyroidism, toxic ingestions, and diffuse structural lesions.

It may be difficult to distinguish classic metabolic triphasic waves from epileptiform discharges with a triphasic morphology. Particularly when repetition rates are high, triphasic waves may mimic EEG patterns of NCSE *(76)*. Although an EEG response to administration of benzodiazepines can be helpful in confirming a diagnosis of NCSE, benzodiazepines may also abolish typical triphasic waves *(10)*. Triphasic waves, often sharply contoured, may appear as patients are tapered from pentobarbital (Fig. 24) *(77)*. Such patterns complicate management decisions in patients with refractory SE.

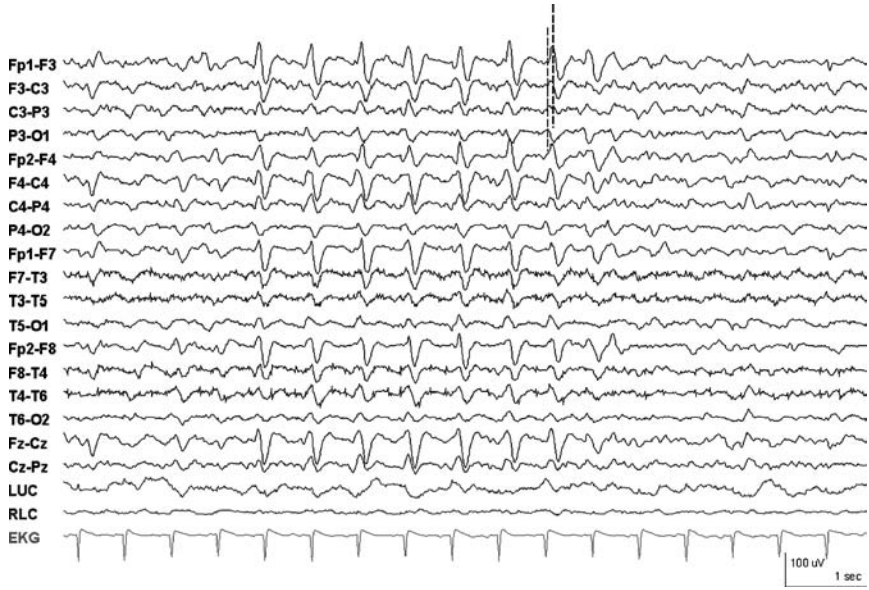

Fig. 23. Triphasic waves in a 53-yr-old woman with hepatic encephalopathy. Note the posterior to anterior lag in the initial positive component of the triphasic wave (dashed lines) and the slow frequency (<2 Hz).

3.5.5. Burst Suppression

Burst suppression is rarely confused with SE patterns, but is included here because it may be the goal of treatment of refractory SE with general anesthetic agents *(78)*. Burst suppression consists of two alternating EEG patterns (Fig. 25). One- to 2-s bursts of generalized high-voltage delta and theta activity, often intermixed with epileptiform discharges, occur every 2 to 10 s. These are separated by periods of background suppression, with low-voltage or nearly flat theta and delta activity, ranging in length from 2 s to minutes *(79)*. Burst-suppression patterns are commonly seen with hypoxic-ischemic encephalopathies, severe hypothermia, intoxication with CNS depressants, and deep barbiturate anesthesia. When used to titrate general anesthesia for treatment of SE, a burst:suppression ratio of 1:3–4 is a typical goal.

4. INDICATIONS FOR EMERGENCY EEG FOR DIAGNOSIS OF STATUS EPILEPTICUS

EEG is not necessary to make a diagnosis of SE in most patients with convulsive movements, but patients who have received neuromuscular paralytic agents, patients with suspected NCSE, and patients with possible psychogenic SE require EEG for accurate diagnosis. Emergency (24-h) EEG is available in 80% of accredited EEG laboratories, but there may be a delay from 3 to 24 h between initial request and

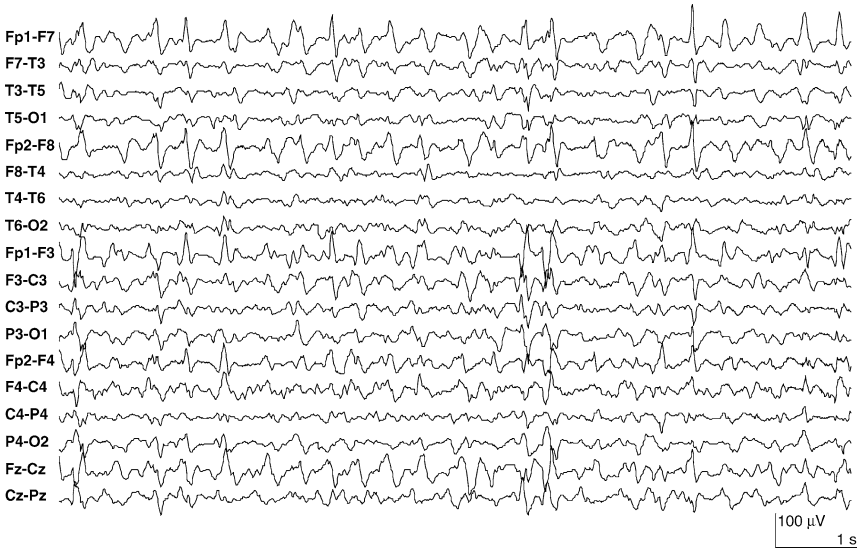

Fig. 24. A pattern of triphasic waves resembling generalized SE appeared during taper of pentobarbital for refractory partial SE. The triphasic waves sometimes occurred at a rate of 3 Hz and often showed very sharp (epileptiform) morphology. Pentobarbital was initially restarted when this pattern appeared; when it reappeared upon tapering pentobarbital again, the drip was not restarted. The triphasic waves resolved spontaneously 18 h later.

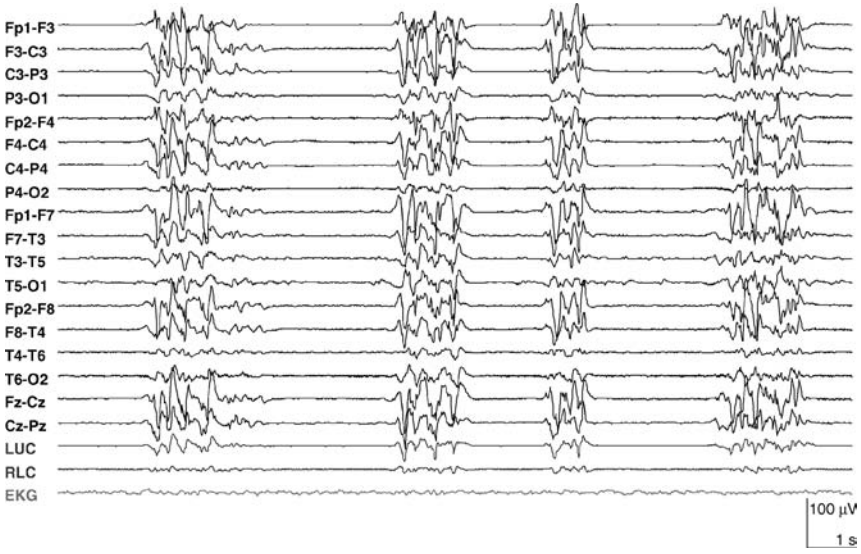

Fig. 25. Burst suppression pattern in a 15-yr-old boy with severe head trauma and SE. EEG shows bursts of moderate voltage sharp and slow wave activity lasting 2 to 5 s, alternating with periods of severe generalized background suppression lasting 5 to 20 s.

interpretation *(80)*. Most centers approve emergency EEGs for suspected NCSE (100%), treatment of SE (84%), and diagnosis of convulsive SE (75%) *(80)*.

NCSE is frequently unrecognized, and is probably significantly underdiagnosed *(47,81,82)*. EEG should be performed in all patients with alterations in consciousness of unknown etiology. The EEG is particularly important for the diagnosis of SE in critically ill patients, in whom concurrent neurologic deficits, sedation, or neuromuscular blocking agents confound the diagnosis of seizures. Up to 35% of neurologic intensive care unit (ICU) patients have nonconvulsive seizures, 76% of whom have NCSE *(9)*. Patients with brain insults are particularly likely to have nonconvulsive seizures; continuous EEG monitoring has revealed subclinical electrographic seizures in 16% of patients with severe head trauma *(83)* and 12% with intracerebral hemorrhage *(84)*. Electrographic seizures may be present in 8 to 37% of comatose or obtunded patients with no or subtle clinical motor signs *(85–87)*.

5. MONITORING OF TREATMENT EFFICACY

One of the most important clinical applications of EEG is its use in guiding treatment of SE to avoid under- or overtreatment. Persistent NCSE can increase cerebral blood flow, intracranial pressure, and oxygen demands, even if clinical signs are absent *(88)*. Overaggressive therapy, on the other hand, can result in hypotension or prolonged mechanical ventilation. EEG monitoring should be performed in patients who remain unconscious after apparent successful treatment of SE or who have refractory SE. EEG appears to be underutilized in management of SE; one UK survey found that only 23% of clinicians used intermittent EEG to monitor treatment efficacy, while 30% used a cerebral function monitor and 45% clinical criteria alone *(89)*. Clinical assessment (e.g., cessation of motor activity and return to normal consciousness) is inadequate in determining treatment success. In the VA Cooperative study, only 17% of patients with overt GCSE and no patients with subtle GCSE regained normal consciousness within 12 h of treatment *(90)*. Only EEG can distinguish post-GCSE patients who are in drug-induced coma from the 14 to 20% with continued NCSE *(21,90)*. Subclinical electrographic seizures that last for less than 30 min are even more common, occurring in approx 50% of patients after GCSE *(21,91)*. EEG is also essential to detect withdrawal seizures, occurring in up to 68% of patients, as general anesthesia is tapered *(91)*.

Therefore, patients with refractory SE or persistently impaired mental status after treatment require continuous or periodic monitoring of the EEG tracing at the bedside. Optimally, EEG monitoring should be performed continuously from the time aggressive therapy (i.e., general anesthesia) is started, until the patient is successfully weaned and awakens. EEG should be reviewed immediately at the bedside until SE is stopped or burst suppression is induced. Frequency of further EEG monitoring is dictated by the patient's condition; if seizures are suppressed, less frequent evaluation may be sufficient, while continued or recurrent seizures require more intensive monitoring. If continuous EEG is not available, daily EEGs or periodic sampling are alternatives, but they may miss infrequent subclinical seizures. Accurate interpretation of the EEG patterns often requires concurrent video monitoring or direct assessment of the patient.

Several protocols exist for treatment of refractory SE *(91–95)*, but the optimal depth and duration of therapy are uncertain. The usual endpoint of pentobarbital treatment of SE is a burst-suppression pattern, with interburst intervals ranging from 3 to 30 s *(95–97)*. Breakthrough seizures can occur even if burst suppression is achieved. Deeper levels of anesthesia to produce a complete suppression pattern ("flat" EEG) may improve SE control and survival *(98)*. Burst suppression may be more difficult to achieve with midazolam and propofol; with these drugs, seizure suppression is the treatment goal *(60)*. This usually requires continuous EEG monitoring. Tapering of anesthesia should be monitored with EEGs repeated every 6 to 12 h until seizure activity does not return.

6. EEG AND PROGNOSIS OF STATUS EPILEPTICUS

After-SE ictal discharges (ASIDS), ictal patterns consisting of rhythmic discharges (spikes, sharp waves, or spike wave discharges) that last 10 s to minutes, occur in 48% of patients with GCSE *(21)*. ASIDS meeting criteria for NCSE were associated with higher mortality rates, even after controlling for age and etiology of SE, while delayed ictal discharges (DIDs) recurring more than 30 min after SE is completely controlled did not worsen outcome. A normal EEG after SE predicted a good outcome, with zero mortality and morbidity *(21)*. The presence of GPEDs late in SE were associated with poor outcome in one study *(22)*, but not in another *(28)*. The duration of NCSE was significantly related to poor outcome in one study, with mortality rates of 36% if seizures were stopped within 1 h, but 75% if seizures persisted for more than 24 h *(8)*.

7. TECHNICAL ASPECTS OF EEG IN STATUS EPILEPTICUS

Monitoring SE with EEG is technically demanding. Electrode integrity can be difficult to maintain, necessitating use of needle electrodes or disk electrodes affixed with collodion. Artifacts in the electrically hostile ICU environment often obscure the EEG, making accurate interpretation problematic. Large amounts of EEG data are generated and must be interpreted quickly to facilitate patient care. Rapid bedside interpretation is aided by automated analysis of digital EEG. This final section summarizes some of the technical challenges of EEG monitoring for SE.

7.1. Digital EEG and Networking

While intermittent paper EEG recordings can be used to monitor SE, continuous digital EEG greatly facilitates data management and review. Digital EEG machines allow post-recording adjustment of montages, sensitivity and filters, acquisition and storage of large amounts of data, off-site EEG review over a network, quantitative data analysis, and automated spike and seizure detection. For continuous EEG to be useful in clinical decision-making, records must be reviewed and interpreted by trained personnel many times a day. ICU nurses can be trained to recognize seizures at the bedside. Seizures are often missed on bedside recordings, however; in one study only 40% of nonconvulsive seizures were visually detected online, with the remainder found at later review *(9)*. Attaching EEG machines to the hospital network

allows EEG technologists and electroencephalographers to access real-time EEG from a variety of locations over the hospital intranet or the Internet.

7.2. Artifacts

A variety of artifacts complicate interpretation of continuous EEG recordings, including patient movements, skull defects and scalp edema, intensive care unit equipment, electrical noise, and nursing interventions. Careful attention to electrode integrity and use of collodion or needle electrodes can reduce some artifact. An optically isolated headbox and 60-Hz notch filters may limit electrical 60-Hz interference. Some ICU equipment such as hemoperfusion pumps and percussion beds produce rhythmic EEG waveforms that may mimic seizures. Stimulation and spontaneous arousals may produce periodic or ictal-appearing patterns. Accurate interpretation is facilitated by staff notations of patient movements or nursing interventions on the EEG record or by concurrent video recording.

7.3. Automated Analysis Techniques

7.3.1. Seizure Detection Algorithms

Automated event detection identifies segments of EEG that contain particular events of interests, such as epileptic spikes or seizures. Several commercially available algorithms can be used to recognize a wide variety of seizure patterns. Algorithms usually are designed to identify paroxysms of rhythmic activity with increased amplitude or frequency compared to background activity *(99,100)*. Parameters such as frequency (usually 3–20 Hz), field, and amplitude can be adjusted to refine detections. Alternatively, artificial neural networks can be trained to detect events by presenting many samples representative of seizures and nonseizures, and the neural network learns to separate the two groups *(101)*.

The computer flags possible events for later review (Fig. 26). Automatic detection algorithms do not detect all electroencephalographic seizures and often falsely flag artifacts as possible seizures. This can be particularly problematic with long-term EEG recordings such as those made in the ICU. In addition, currently available software has been trained and validated primarily on samples obtained from epilepsy monitoring units and ambulatory epilepsy patients. Seizures in patients with SE or acute brain injuries are very different, with poor organization, slower frequencies, long duration, and unclear onsets and offsets. New software trained on patients with acute brain injury will increase utility of detection algorithms in the ICU *(102,103)*. Automated event detection is therefore useful to reduce the amount of data that must be reviewed, but it cannot substitute for a trained electroencephalographer.

7.3.2. Quantitative EEG

Computerized EEG analysis that displays EEG activity as a graph over time can improve nonelectroencephalographer interpretation of continuous EEG *(7,104)*. Quantitative EEG uses fast Fourier transformation to separate digital EEG signals

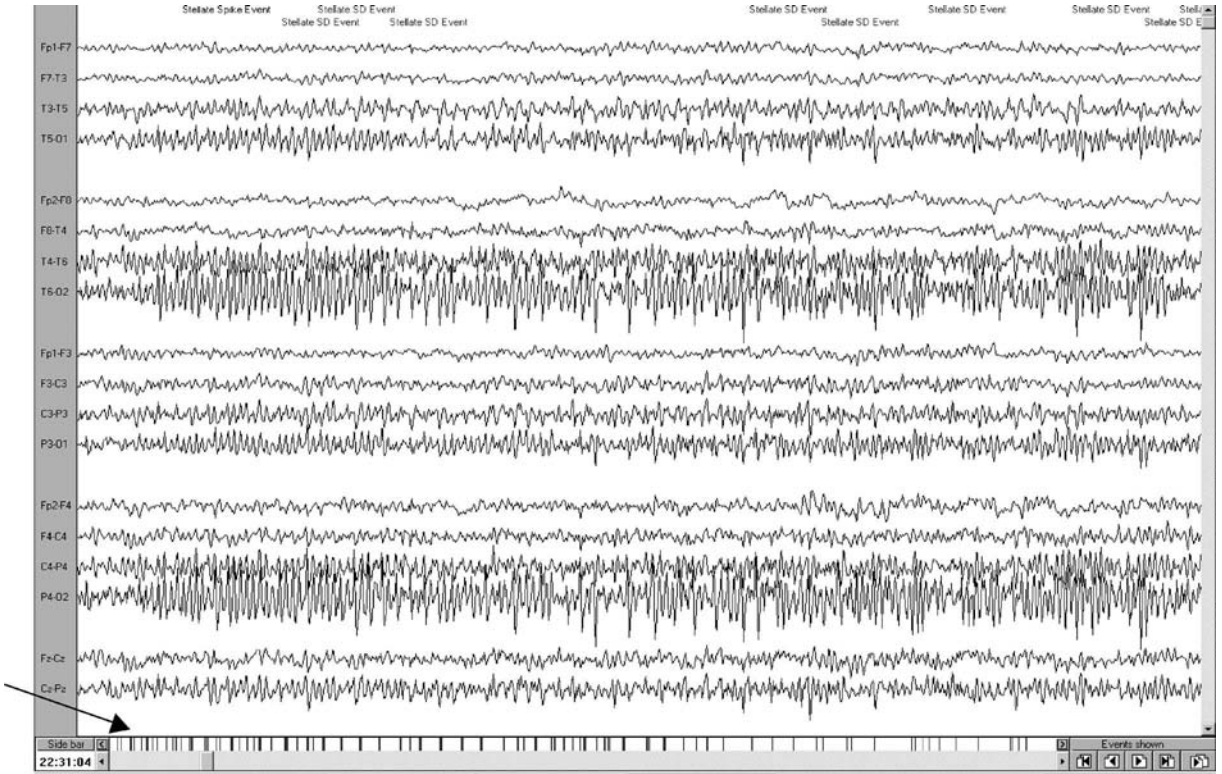

Fig. 26. Automated seizure detection in monitoring of SE. This 30-yr-old woman with mild mental retardation and intractable epilepsy was admitted with lethargy and intermittent head and eye deviation to the right. EEG showed frequent electrographic seizures beginning with rhythmic beta activity in the right occipital region, gradually increasing in amplitude and spreading to the right posterior temporal region and left occipital region (T6-O2, P4-O2). Continuous EEG monitoring with automated seizure detection shows frequent seizures over an 8 h period. Each vertical line on the seizure detection bar at the bottom (arrow) indicates an automatic detection of an electrographic seizure similar to the one displayed here.

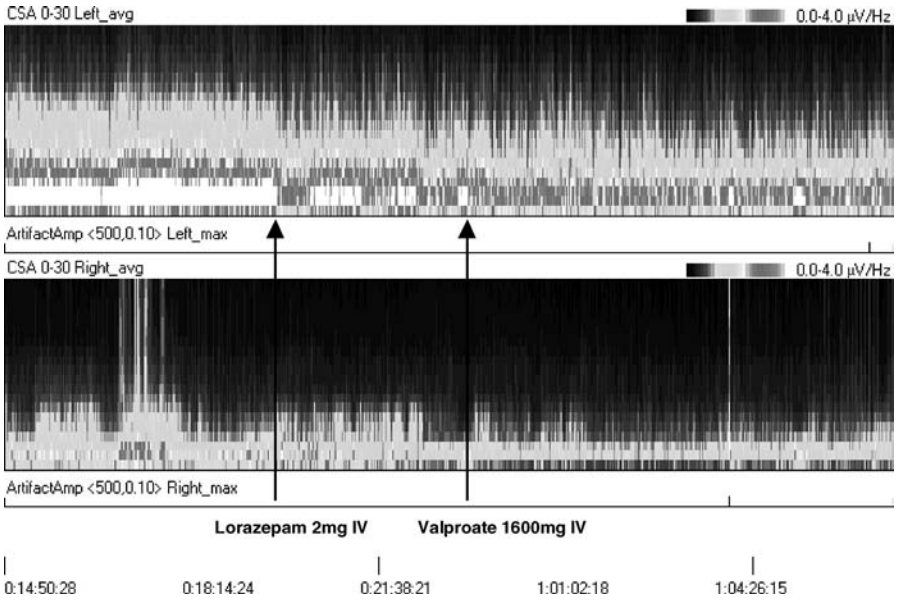

Fig. 27. Compressed spectral analysis (CSA) in monitoring of SE. See text for detailed description of CSA. Left hemisphere is displayed in top panel, right hemisphere in bottom panel. Initial EEG showed large amounts of delta "power," indicated by white areas in the top panel, corresponding to continuous electrographic seizures arising from the left temporal region, while the right hemisphere (shown on bottom) is normal. After administration of iv lorazepam (arrow), ictal activity ended, but soon recurred with decreased frequency, indicated by lower amounts of delta power. After administration of intravenous valproate (second arrow), ictal activity ceased and did not recur. This CSA was not able to detect individual seizures, which occurred frequently and were of brief duration.

into their component frequencies and amplitudes, called "power." Compressed spectral array (CSA) is the most commonly used graphical display for EEG data. EEG power data for single channels or combinations of channels over each hemisphere are displayed as color graphs of power (e.g., total power, power in certain frequency bands, ratios of power in certain bands to total power, etc.) vs time (Fig. 27).

Review of graphical displays allows rapid detection of even subtle changes in EEG activity over long periods of time, rather than review of hundreds of pages of raw EEG data (Fig. 28). The associated raw EEG must be immediately available for review, however, as power changes can be caused by seizures, periodic patterns, changes in sleep/wake states, arousals, or artifacts. The specific cause of the power change cannot be determined by reviewing the CSA graph. CSA display of certain frequency bands, usually theta and alpha frequencies, can be used to detect seizures (Fig. 29). Graphs of CSA aid in bedside interpretation of EEG by staff unfamiliar with raw EEG interpretation. Such staff can then notify EEG technologists or electroencephalographers to review the sections of EEG in question.

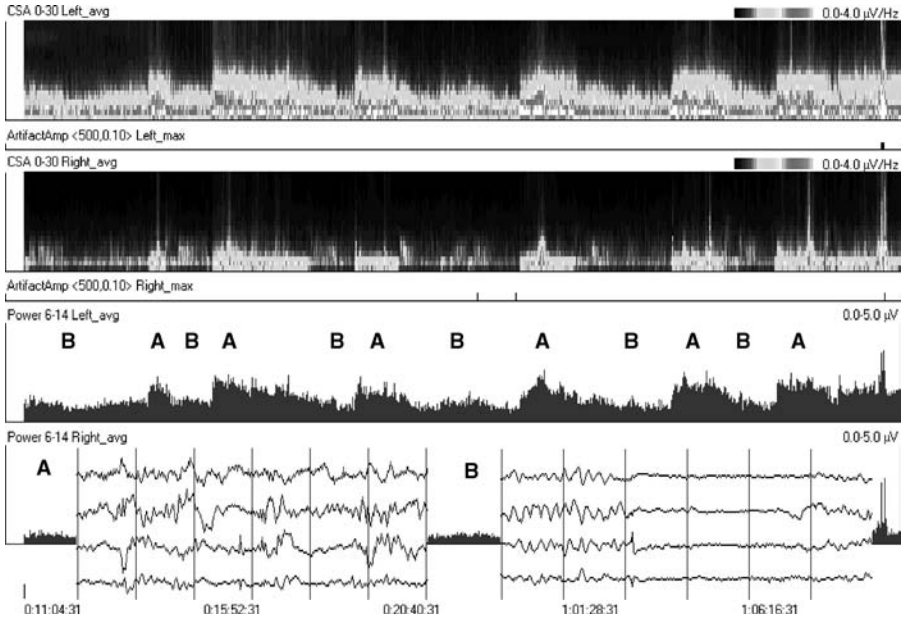

Fig. 28. CSA for monitoring of treatment efficacy in a patient on a midazolam drip for SE (top two panels). CSA in the third panel showed two main "states:" **A,** high theta power, and **B,** low theta power. The insets below show raw EEG segments corresponding to each of these CSA patterns: **(A)** left hemisphere periodic lateralized epileptiform discharges; and **(B)** a burst suppression pattern with low voltage theta activity alternating with background attenuation. No seizures occurred during this recording.

8. SUMMARY

EEG is an essential tool for the diagnosis, classification, and monitoring of SE. A wide variety of EEG patterns can be seen in SE, reflecting different seizure types, etiologies, and seizure duration. While most GCSE can be diagnosed based on clinical manifestations, EEG can be used to differentiate GCSE from psychogenic SE, and to detect persistent NCSE following apparent successful treatment of GCSE.

Fig. 29. CSA for monitoring of SE. **(A)** CSA 2 h following successful treatment of GCSE shows intermittent generalized increases in power in the 6–14-Hz band (third and fourth panels), corresponding to generalized electrographic seizures. Seizures stopped after initiation and titration of pentobarbital to a burst suppression pattern. Seizures later recurred several times, as indicated by later increases in 6–14 Hz power, requiring progressive increases in pentobarbital dose; lower part of figure shows one such seizure recorded. **(B)** Pentobarbital was eventually increased to achieve complete suppression of the background. Despite this, frequent electrographic seizures (increase in 6–14 Hz power; two lower panels) recurred and were refractory to pentobarbital and later thiopental. **(C)** EEG of the generalized electrographic seizures seen in **B**.

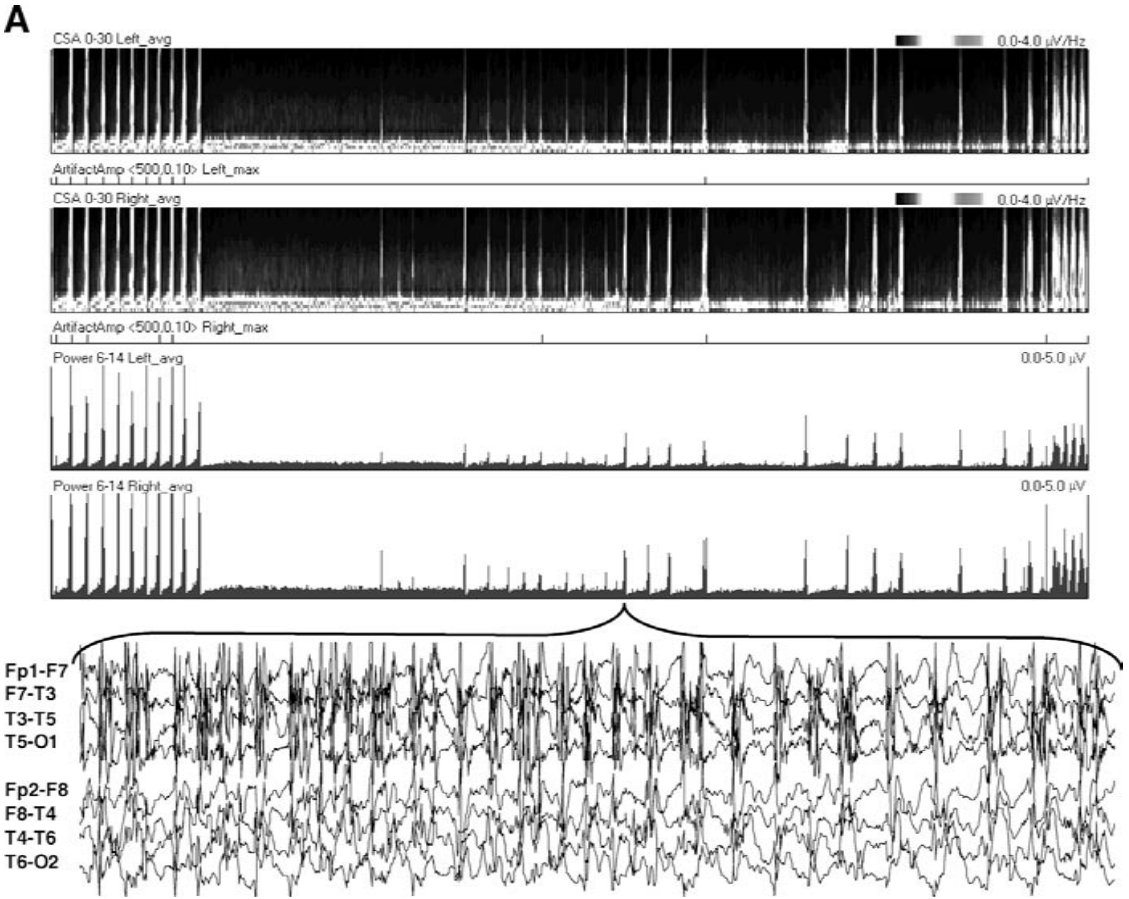
A
CSA 0-30 Left_avg
0.0-4.0 µV/Hz
ArtifactAmp <500,0.10> Left_max
CSA 0-30 Right_avg
0.0-4.0 µV/Hz
ArtifactAmp <500,0.10> Right_max
Power 6-14 Left_avg
0.0-5.0 µV
Power 6-14 Right_avg
0.0-5.0 µV
Fp1-F7
F7-T3
T3-T5
T5-O1
Fp2-F8
F8-T4
T4-T6
T6-O2

Fig. 29.

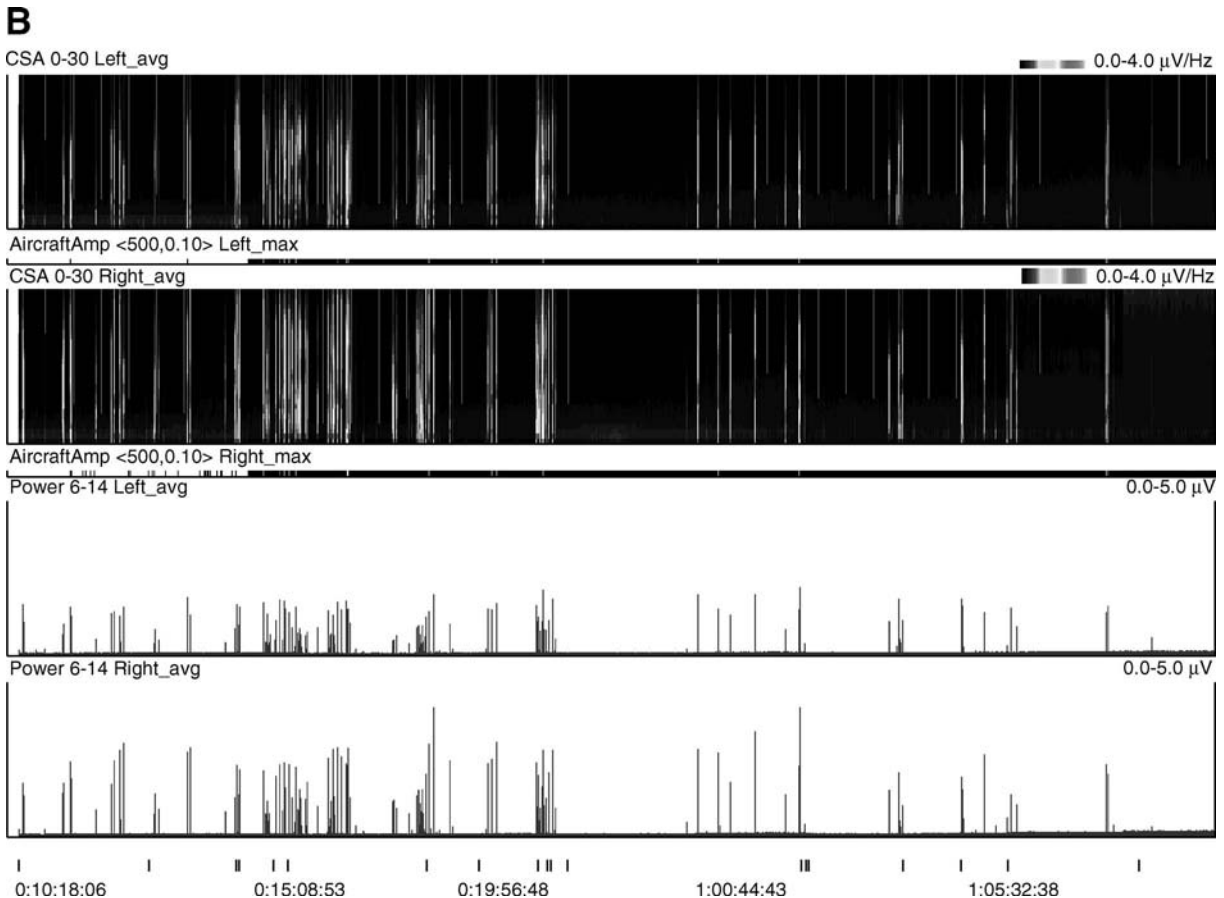

Fig. 29. *(Continued)*

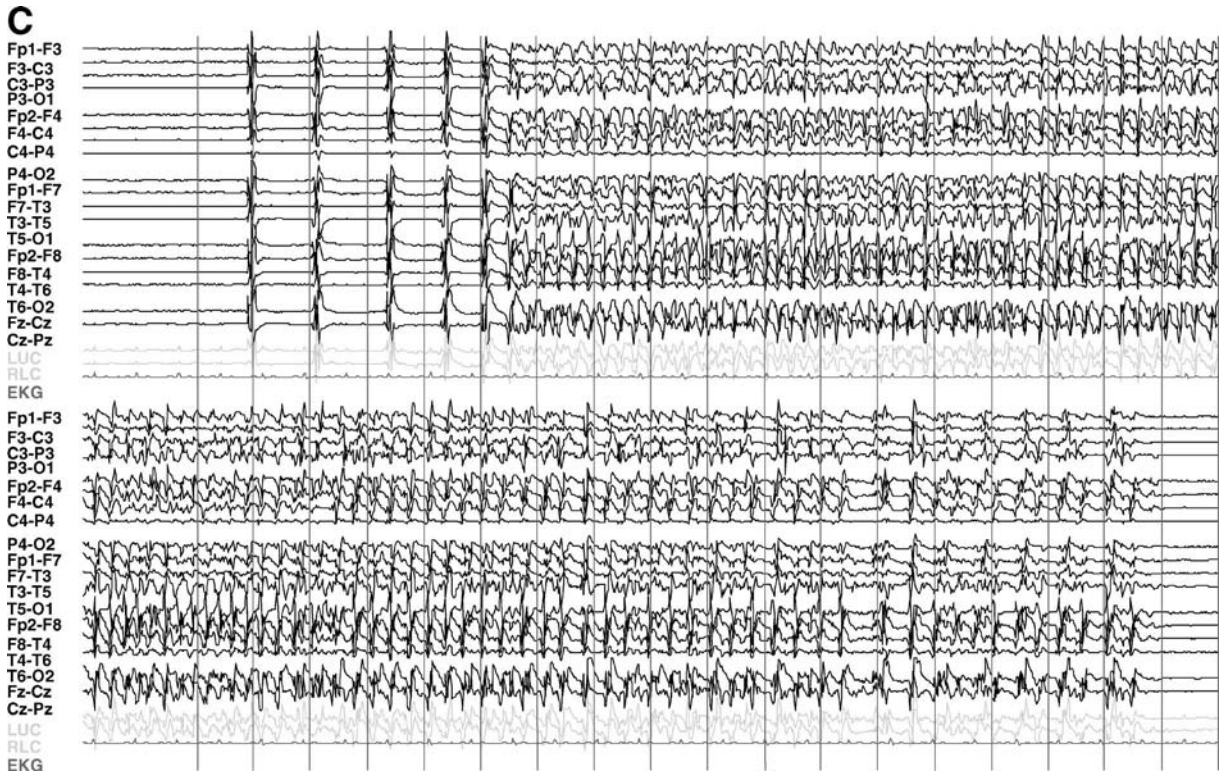

Fig. 29. *(Continued)*

EEG is most useful in the diagnosis of NCSE, where clinical signs may be confusing or absent. Periodic EEG patterns may mimic SE, making diagnosis more difficult. Continuous or periodic EEG monitoring is essential to confirm treatment efficacy in patients who remained confused after AED treatment and those who have refractory SE. Analysis of continuous EEG recordings can be aided by automated seizure detection algorithms and by quantitative EEG methods.

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II Generalized Convulsive and Focal Status Epilepticus

6

Generalized Convulsive Status Epilepticus

Causes, Clinical Manifestations, and Consequences

Bernard S. Chang

1. INTRODUCTION

Generalized convulsive status epilepticus (GCSE) is the most clinically dramatic and medically dangerous form of status epilepticus (SE). GCSE is characterized either by continuous bilateral convulsive activity or by generalized convulsive seizures that recur without significant recovery between them. Although GCSE can in fact begin with a single partial seizure or partial SE, and although the visible convulsive activity normally decreases in intensity and frequency with time, the cardinal feature of GCSE remains the widespread clonic movements of the extremities. In simplified classification schemes of SE, GCSE is usually contrasted with nonconvulsive SE and with partial or focal SE *(1,2)*.

Proper management of GCSE requires an understanding of its potential underlying causes, its clinical manifestations, and the short- and long-term consequences of an episode of GCSE. This chapter will present an overview of these topics, linking evidence from the literature to lessons for clinical practice whenever appropriate. Other topics relevant to GCSE, including the electroencephalographic (EEG) features and pharmacologic treatment of this condition, are reviewed elsewhere in this volume.

2. CAUSES

GCSE can arise from a number of different underlying etiologies. The identification of the correct cause in any particular case of GCSE is of tremendous clinical importance for two reasons: Treatment of the underlying cause may be critical to successful management of the episode, and the prognosis of GCSE is dependent largely on the etiology. Despite this importance, in practice it can be quite difficult to identify a single etiology in any particular case with certainty, due to the acute setting in which GCSE often arises, the difficulty with obtaining history if no corroborative information is available, and the numerous intensive interventions that are used in the management of GCSE.

From: *Current Clinical Neurology: Status Epilepticus: A Clinical Perspective*
Edited by: F. W. Drislane © Humana Press Inc., Totowa, NJ

Broadly, GCSE occurs in four common situations: in patients with a known seizure disorder or epilepsy (from whatever cause), in patients for whom it is the initial manifestation of epilepsy, in patients who have suffered acute neurologic insults, and in those who have suffered acute systemic insults. Potential etiologies in each of these settings will be discussed in turn.

2.1. GCSE in the Setting of an Existing Seizure Disorder

GCSE is one of the most medically serious complications of epilepsy; proper recognition of its importance in the epilepsy population is critical for patients, caregivers, and physicians. The exact frequency with which GCSE occurs in patients with a known seizure disorder varies widely across reports *(3)*; in one estimate at least 15% of patients with known epilepsy will suffer from an episode of GCSE at some point in their lives, with younger age, genetic cause of epilepsy, and acquired brain insults among the factors causing increased risk *(4)*. Conversely, a large proportion of reported GCSE cases arises in patients with known epilepsy, with reports ranging from about one third *(5)* to more than half *(6)*. In any case, the clinician confronted with a patient in GCSE should look quickly for evidence of a known diagnosis of epilepsy (e.g., medical alert bracelet, anticonvulsant pill bottles).

Epilepsy syndromes include both localization-related (partial or focal onset) and primary generalized (idiopathic) disorders. Because GCSE can begin with a partial-onset seizure or partial SE, it can occur in patients with epilepsy syndromes of either type. In fact, most GCSE in adults appears to be of focal origin *(7)*, a fact consistent with the overwhelming predominance of partial-onset epilepsy in this age group. Some authors have suggested that GCSE arising in patients with idiopathic generalized epilepsy syndromes may present with slightly different seizure characteristics and require different treatment strategies from that arising in patients with partial-onset syndromes *(8)*.

For patients with known epilepsy, the list of potential triggers for an episode of GCSE is long and essentially recapitulates the list of well-recognized triggers for any seizure exacerbation. In particular, alcohol use, intercurrent illness, sleep deprivation, and medication noncompliance appear to be common factors *(6,9)*.

2.2. GCSE as Initial Manifestation of Seizure Disorder

In some instances, patients have GCSE as the only epileptic seizure in their lives. In many cases, patients may develop epilepsy as a *result* of their GCSE, with recurrent unprovoked seizures after the episode of SE. (This is discussed in Section 4.2.1.) For some patients, however, GCSE serves as the initial presentation of an already underlying seizure disorder. The proportion of such cases is difficult to estimate accurately because it is only subsequent history or diagnostic testing that might reveal the presence of a prior tendency toward seizures. Admittedly, such a presentation cannot always be reliably distinguished from epilepsy arising as a result of GCSE, but certain features such as primary generalized epileptiform features

on EEG or a strong family history of epilepsy can suggest the presence of an underlying epileptic disorder. Epidemiologic reports describe that about 12% of patients with epilepsy have SE as their initial presentation *(10)*, although this figure does not of course distinguish between cases in which signs of earlier epilepsy were present and those in which they were not. In either case, clinicians caring for patients with a history of GCSE must recognize the increased risk for subsequent seizures, no matter what the attributable cause.

2.3. GCSE in the Setting of Acute Neurologic Insults

For several reasons, it is appropriate to focus in detail on the various acute neurologic and systemic insults that can lead to GCSE. First, these make up a large proportion of GCSE cases, as seen below. Second, by their nature these are more likely to be cases presenting to the non-neurology and non-epilepsy specialist, who may not be as familiar with GCSE diagnosis and management. Third, in addition to the use of anticonvulsants, which by themselves are usually the appropriate treatment for GCSE arising in the two previously described settings, in these cases additional management of the underlying insult is usually required for proper treatment of the patient's condition. Finally, GCSE may be more difficult to recognize in these settings because its clinical features may be superimposed on signs arising from the underlying neurologic or systemic condition (e.g., GCSE in the setting of dense hemiplegia from a carotid distribution stroke).

2.3.1. Acute Stroke

GCSE is an uncommon but serious complication of acute cerebral infarction. Broadly, SE (including all types) is reported to occur in only 1 to 2% of stroke cases in large series *(11–13)*, although conversely stroke is responsible for a significant proportion (22%) of all cases of SE *(14)*. Postinfarct seizures and SE are generally divided into those of early onset (occurring within 7 d after stroke) and those of late onset (occurring thereafter). One review of poststroke SE found that stroke types were evenly divided in the early-onset cases, but ischemic strokes and posterior cerebral artery strokes were more common in the late-onset cases *(12)*. In this series, nonconvulsive SE was actually more common than GCSE in the early-onset group. Another, larger series of poststroke seizure patients found that SE was more common in stroke patients with higher disability, but surprisingly the risk of SE did not appear to be associated with stroke type, cause, lesion size, or cortical involvement *(13)*. In total, 9% of poststroke seizure patients in this series had SE.

It is thus important for the clinician caring for stroke patients to recognize that GCSE is a potential complication of acute cerebral infarction, and that there may not be obvious factors that help predict which patients will develop GCSE compared to those who will develop uncomplicated postinfarct seizures. In addition, for the physician approaching a GCSE case of unknown etiology, especially in an older patient or one with vascular risk factors, acute stroke should be strongly considered

in the differential diagnosis of underlying causes, particularly if an earlier seizure disorder does not appear to be present.

2.3.2. Head Trauma

Traumatic brain injury (TBI), a leading public health problem even independent of its potentially epileptogenic effect, is responsible for a large proportion of new-onset seizures in adults *(15)*. The risk of posttraumatic seizures, either in the early stage (within 7 d after injury) or in the late stage (thereafter), depends on a number of factors, primarily the severity of head injury *(16)*. It is now generally recognized that the development of late posttraumatic seizures cannot be prevented by the prophylactic administration of anticonvulsants *(17,18)*. Although simple posttraumatic seizures have been studied in detail, the exact frequency or nature of GCSE occurring after acute TBI is unclear. Craniocerebral trauma is responsible for anywhere from 1 to 26% of all cases of SE in various series *(5)*, although this figure may include remote traumatic injuries as well as acute ones. Clinicians caring for patients suffering from acute head injury need to have a particularly heightened awareness of the risk for GCSE in this setting, given the clearly deleterious effect of GCSE on recovery from head injury as well as the increased risk of toxicity from anticonvulsants in this population *(19)*.

2.3.3. Brain Tumors

Cerebral neoplasms increase the risk of seizures. A directed review of malignant gliomas (glioblastoma multiforme and malignant astrocytomas) found that seizures were commonly refractory, but no episodes of GCSE developed among 65 such patients (although 10 episodes of focal motor SE did) *(20)*. Conversely, in a large population-based epidemiologic study of GCSE in California, tumors accounted for 1.8% of cases *(21)*, while another large population-based series from Richmond, Virginia found tumor to be responsible for 7% of adult SE cases *(22)*.

2.3.4. Demyelinating Disease

Seizures also occur with greater frequency in patients with multiple sclerosis than in the general population *(23,24)*. In almost all cases the seizures are of partial onset, consistent with the focal or multifocal nature of the subcortical demyelinating plaques in this disease. While most patients with multiple sclerosis and associated epilepsy have well-controlled seizures, there are at least several reported cases of focal motor SE (epilepsia partialis continua) *(23,24)*. GCSE, by contrast, appears to be seen rarely—in one review of 268 multiple sclerosis patients (20 of whom had seizures), only one had convulsive SE *(23)*. In the largest reported series, of more than 5000 multiple sclerosis patients (of whom only about 1% had seizures), no cases of GCSE were noted *(24)*. Thus, while focal motor SE can be a concern in patients with multiple sclerosis, GCSE appears to be a rare complication. One population-based epidemiologic study showed that 1.0% of all GCSE patients carried a diagnosis of multiple sclerosis *(21)*.

2.4. GCSE in the Setting of Acute Systemic Insults

2.4.1. Metabolic Causes, Hypoxia, Anoxia, and Organ Failure

Patients with a wide range of acute metabolic insults (or acute changes superimposed on chronic conditions) can develop GCSE. Often these situations occur in hospitalized patients on the medical ward; a review of 41 cases of SE (including all types) that developed *de novo* in hospitalized patients found that a significant metabolic disturbance was present in more than half *(25)*. Electrolyte imbalance, renal disease, hepatic disease, and hypoxia were all implicated, with some patients having more than one of these conditions concurrently. Naturally, the rates of metabolic derangements are much lower in population-based series of SE—in the large California series, 8.7% of GCSE cases were potentially related to "sodium imbalance" while another 8.0% were potentially related to anoxia *(21)*. In the population-based series from Virginia, GCSE was attributed to a metabolic etiology in 15% of adult SE cases, while hypoxia or anoxia accounted for an additional 18% *(22)*.

Two lessons for clinical practice are worth noting: first, it is important to search for metabolic abnormalities in GCSE patients, both those with earlier epilepsy and those without (as electrolyte abnormalities and other metabolic disturbances may be a precipitant for seizure exacerbation in epilepsy patients), because appropriate correction of the metabolic abnormality may be necessary to abort the episode of SE. As just one example, one reported case of hepatic encephalopathy and SE was refractory to standard anticonvulsants but eventually resolved after administration of lactulose *(26)*. Second, there is the potentially difficult but important task of differentiating between metabolic abnormalities that could be sequelae of GCSE from those that are likely to be contributing causes. For example, low serum bicarbonate and acute renal failure are both potential complications of GCSE (related to lactic acidosis and rhabdomyolysis, respectively), but both could also arise from alternative causes and be potential contributing etiologies to an episode of GCSE.

2.4.2. Infections

Infections are responsible for another subgroup of GCSE cases associated with acute systemic insults. Although acute meningitis and encephalitis are relatively uncommon causes of GCSE, they deserve particular mention because of the necessity of appropriate antimicrobial treatment in the management of SE caused by these infections. In the two large population-based series of SE from California and Virginia, primary central nervous system (CNS) infections accounted for only 0.6% and 3% of cases, respectively *(21,22)*.

In addition to primary CNS infections, systemic sepsis can also be a potent trigger of GCSE. In the small series of SE cases developing *de novo* in the hospital, 12% were associated with underlying sepsis *(25)*, and in the large Virginia series, 7% of adult SE cases were associated with "infection" not further specified *(21)*. For practical purposes in many cases, of course, a single decisive factor may not be able to be identified, because sepsis, hypoxia, electrolyte imbalances, and organ failure are likely to coexist.

2.4.3. Toxins

Among toxin-induced cases of GCSE, alcohol is the most common offender. Alcohol was identified as a potential contributing factor in 13% of adult SE cases in Virginia *(22)* and "alcoholism" was found in 8.1% of cases in the population-based California GCSE series, although acute alcohol intoxication in the absence of long-standing alcoholism was not described *(21)*. In an urban hospital-based series of 249 patients with GCSE, 10.8% had alcohol abuse as the only identifiable precipitating cause *(27)*. In 44% of these cases, GCSE turned out to be the initial presentation of alcohol-related seizures. The majority of alcohol-related GCSE cases were discharged from the hospital with no new neurologic deficits. Perhaps most interestingly, this series found that alcohol-related GCSE patients did not differ from a comparison group with isolated alcohol withdrawal seizures with regard to their history of alcohol abuse. For clinical practice, there is now good evidence that benzodiazepines are the most useful agents in both the primary and secondary prevention of alcohol withdrawal seizures (and presumably by extension, alcohol-related GCSE) in susceptible patients *(28)*.

3. CLINICAL MANIFESTATIONS OF GCSE

The importance of recognizing the clinical manifestations of GCSE cannot be overstated. Although it would appear that recognition of the features of GCSE would be straightforward, in fact the outwardly visible manifestations may be obvious only in the initial phases of the episode; with time these signs decrease in intensity and may become less well-defined. The signs of prolonged GCSE thus merit particular attention due to their more subtle nature. (There are also electroencephalogram [EEG] manifestations of GCSE and other forms of SE. Those of GCSE are often very characteristic, and while not usually necessary in making a diagnosis of GCSE, they are instructive in learning about the physiology and are related to the clinical signs of SE described here. EEG features of GCSE and other forms of SE are detailed in Chapter 5.) The core clinical features of GCSE can be divided into outwardly visible signs and nonobservable systemic manifestations.

3.1. Outwardly Visible Signs

The observable signs of GCSE depend on whether the patient is suffering from GCSE of the "continuous" type, in which convulsions are ongoing, or whether he or she is having frequent recurring generalized convulsive seizures without full recovery in between *(29)*. The generalized tonic-clonic (GTC) seizure that heralds the onset of GCSE at first may appear no different from any typical GTC seizure. There is an initial tonic phase in which the extremities stiffen without significant shaking, an "epileptic cry" may be emitted due to pharyngeal tonic spasm and chest wall contraction, and urinary incontinence may occur. After the tonic phase, which lasts about 10 s, widespread, fairly symmetric, rhythmic clonic movements of the extremities then supervene. In a normal, spontaneously terminating GTC seizure, these clonic movements gradually taper in frequency, increase in amplitude, and

eventually peter out, with a postictal state to follow in which the patient is variably confused or fatigued for minutes to hours.

In continuous convulsive cases of GCSE, these convulsive movements do not resolve spontaneously. In some cases, quite visible convulsions continue and the diagnosis of GCSE will continue to be obvious. In most cases, however, these movements attenuate somewhat and lead to an ongoing period of less obvious rhythmic movements, sometimes involving only limited clonic jerks of parts of the extremities, abdominal muscles, or face. There may be isolated nystagmoid movements of the eyes. This phase has been termed a more "subtle" stage of GCSE *(30)*. A complete resolution of these movements would be defined by some authors as a progression into nonconvulsive SE, so that in ongoing GCSE some visible motor activity should be seen to continue. However, such movements may be quite minimal, and the distinction between convulsive and nonconvulsive SE at this point may be an arbitrary one. A detailed description of the stages of EEG changes during typical GCSE *(31)* is discussed in Chapter 5 but it is worth noting here that the gradual tapering in the frequency of epileptiform discharges in this sequence correlates with the gradually tapering frequency of clinically observed clonic movements.

GCSE that consists of frequent seizures without recovery is, unsurprisingly, clinically recognized by the recurrence of typical GTC seizures. Perhaps the main concern is establishing whether recurrent seizures are truly commencing before the postictal state has ended. The answer may not be immediately apparent if the patient is not under close observation by family members and clinicians or if an underlying neurologic deficit or systemic illness is present, rendering the patient's "baseline" pre-GCSE functioning altered. In any case, if seizures are truly recurring frequently, it is usually appropriate to manage them in a clinically urgent manner, whether criteria for GCSE are specifically fulfilled or not, although there is little published evidence on prognosis in such situations.

As with postictal states following single GTC seizures, those following episodes of GCSE can exhibit a range of severity, from mere somnolence and inattention to outright coma. Not only may GCSE lead to postictal states that are prolonged in duration, but clusters of GTC seizures can also lead to prolonged postictal states, and patients with histories of SE may be susceptible to more prolonged postictal states even after isolated GTC seizures *(32)*. It is critical, however, to record an EEG on any post-GCSE patient who has a prolonged "postictal" confusion to ensure that nonconvulsive SE is not the true cause of the patient's encephalopathy *(33)*.

3.2. Systemic Manifestations of GCSE

Although the outwardly visible clonic movements in GCSE may have the greatest psychological impact on caregivers and can have serious medical consequences (e.g., orthopedic injury and rhabdomyolysis), the underlying systemic manifestations and physiologic changes that accompany GCSE are also important for the physician to understand *(34)*. It can be difficult, however, to differentiate between those systemic manifestations that are treatment-related (e.g., barbiturate-induced hypotension) from those that are truly primary to the condition of GCSE. The major

physiologic effects of GCSE, which occur both early and late in the stages of ongoing convulsive activity, will be discussed below; the complications of GCSE, which develop after the episode has resolved, will be discussed later in this chapter.

3.2.1. Acid-Base Disturbances

Acidosis occurs in a large number of patients with GCSE. Arterial blood gases in 70 patients in GCSE who were not mechanically ventilated and did not have clear metabolic pathology demonstrated that in the vast majority, patients' arterial pH was below the normal range *(35)*. pCO_2 results in this series indicated that both respiratory acidosis and metabolic acidosis were occurring, likely from impaired ventilation and release of lactic acid into the bloodstream from ongoing convulsive muscle activity. Surprisingly, acidosis did not seem to be associated with a greater degree of post-GCSE sequelae, although severely ill patients were not included in this sample because they were ventilated more quickly. There may also, however, be additional unidentified factors (besides convulsions and respiratory difficulties) that contribute to acidosis in GCSE, as acidosis can still be present (although attenuated) in animal models of prolonged seizures even when subjects are paralyzed and mechanically ventilated *(36)*.

3.2.2. Hyperthermia

Elevated body temperature has been found in many but not all patients during GCSE; this has been attributed to the ongoing muscle activity of convulsions *(35)*. In only a small number did the fever signal an infectious etiology of the SE episode. Clinicians should be aware that peripheral blood and cerebrospinal fluid leukocytosis can also be seen with GCSE to some degree *(35)*, and thus they must be cautious in automatically inferring an infectious etiology when these signs are present together with elevated temperature. As with acidosis, it appears that other unrecognized factors may also be partly responsible for hyperthermia, given that it can appear in paralyzed and ventilated experimental animals *(36)*.

3.2.3. Circulatory and Respiratory Changes

With the initial release of catecholamines into the circulation upon the onset of GCSE, systemic arterial pressure and heart rate increase and cardiac arrhythmias may be seen *(34)*. Even fatal arrhythmias may occur *(37)*. In the prolonged phases of GCSE, however, blood pressure begins to fall and may eventually be significantly low. Of course, this is usually the period by which numerous pharmacologic treatments for GCSE have been applied, including those that can lead to iatrogenic hypotension (such as phenytoin and barbiturates). The important question of whether this late drop in systemic arterial pressure might lead to decreased cerebral perfusion relative to cerebral metabolic rate, and thus threaten ischemic neuronal damage, is as yet unresolved.

Among respiratory effects of GCSE, hypoxia is, not surprisingly, seen fairly commonly in both clinical series and experimental animals *(38,39)*, although whether the extent of hypoxia has a substantial effect on outcome or potential brain injury is not clear. There may also be a direct effect of GCSE on the capillary bed in the lung, as

pulmonary edema is one of the most common findings in postmortem examinations following episodes of SE *(40)* and in animal models of prolonged seizures *(41)*. There is some evidence to suggest that pulmonary edema may arise as a result of the autonomic overactivity associated with SE *(34)*.

3.2.4. Electrolyte and Other Metabolic Disturbances

Blood glucose, which initially rises in association with the onset of GCSE and the associated catecholamine release, begins to fall with prolonged GCSE and can even decrease to lower than normal, at least in primate models, as a result of increased insulin secretion in the late stages of convulsive activity *(42)*.

Historically, rhabdomyolysis has been reported after GCSE reaches a relatively prolonged duration, leading to myoglobinuria and then acute renal failure *(43)*. Although the incidence of this complication may be lower in modern times with advances in mechanical ventilation and the use of pharmacologic neuromuscular blockade, it is still reported occasionally, often in association with hyperthermia or in children with genetic disorders of lipid or carbohydrate metabolism *(44)*.

4. CLINICAL CONSEQUENCES OF GCSE

It is well-recognized that GCSE has significant morbidity and mortality associated with it, and the repeated admonitions to physicians to treat GCSE as a true life-threatening emergency stem from experience with patient outcomes following episodes of GCSE arising from many different etiologies and lasting for varying amounts of time. Knowledge of the clinical consequences of GCSE, and what factors predict their appearance (if any), is important not just for the appropriate choice and urgency of treatment but also for prognostication and counseling, rehabilitation planning, and other such aspects of patient care. The common clinical sequelae of GCSE will be presented in turn.

4.1. Mortality

It is a sign of the severity of GCSE that outcome measures usually center around mortality versus survival. There are also nonfatal complications and morbidity, some of which are discussed below, but much of the prognosis is tabulated as mortality. For SE as a whole, mortality rates are high but remarkably varied, depending in large part on etiology and possibly other features. The mortality rate in adults with SE in the large population-based study from Virginia was 26%, a figure representative of most larger series' results *(7)*.

4.1.1. Etiology

Mortality rates in GCSE appear to be influenced by the following factors: etiology, age, and duration. Etiology is the overwhelmingly most important prognostic feature. As seen in the population-based Virginia study and other series, patients with anoxia or multiple medical problems have the highest mortality rates, while those with strokes, tumors, and trauma have an intermediate mortality. Patients with earlier epilepsy in whom GCSE develops due to an exacerbating factor (such as

subtherapeutic anticonvulsant levels, intercurrent illness, or sleep deprivation) generally have the lowest mortality rates. Alcohol-associated GCSE cases tend to have an intermediate or low mortality. Two recent studies have also confirmed these broad principles, both indicating that patients with acute symptomatic causes of GCSE had a much higher mortality than those with prior epilepsy *(45,46)*.

4.1.2. Age

The influence of age on post-GCSE mortality is also clear. In one study, patients older than 60 had a mortality of nearly 40%, while those over 80 had a mortality of nearly 60% *(47)*. At the other end of the spectrum, mortality is typically much lower in children *(48)*. It is evident, however, that etiologies of GCSE differ tremendously among different age groups, and because anoxia, stroke, and concomitant medical illnesses have much higher incidences in the elderly compared to younger age groups, the question of whether age exists as a prognostic variable *independent* of etiology has not been answered definitively.

4.1.3. Duration

Duration may be another predictor of GCSE outcome, but is also likely to be influenced strongly by etiology. In one study, for example, many of the patients with significant long-term sequelae of SE (including death or significant cognitive impairment) came from the group whose SE had lasted more than 2 h before being controlled by treatment *(49)*. Assessing this effect independent from etiology, however, is very difficult. In a series of 200 patients for whom GCSE duration could be established, the investigators attempted to attribute morbidity and mortality to either the SE itself or to the underlying etiology *(6)*. Complications attributed to SE itself appeared to increase significantly when duration exceeded 4 h. The curve of morbidity plotted against duration, however, was uneven and did not increase significantly beyond the 4 h. In the large Virginia series, patients whose SE lasted 60 minutes or more had a 32% mortality rate within 1 mo, compared with a 2.7% mortality in those with shorter durations *(50)*. There was no definite correlation, however, between mortality and duration beyond 60 min. Almost none of the patients died during the episode of SE itself.

A review of 119 patients who had EEGs performed during an episode of SE found that duration longer than 10 h was associated with a worse prognosis; 31% of these patients survived compared to 69% for those with a shorter duration *(51)*. After 10 h, however, the curve of mortality plotted against duration was fairly flat. Many patients with very prolonged SE survived; among these, patients with earlier epilepsy still had better outcomes and those with anoxia had poorer ones. When patients with prior epilepsy (who tended to have shorter SE duration) were eliminated from the analysis, there was no longer a definite benefit from shorter durations, again supporting the hypothesis that etiology may contribute largely to the apparent effect of duration on prognosis.

In summary, etiology appears to be the strongest predictor of mortality in GCSE. The patient's age and duration of GCSE are also associated with survival prognosis,

although whether these effects are independent of etiology is still unknown; it is likely that etiology is responsible for at least a large component of the effect seen with these other two factors. Mortality rates are far from 100% even in the oldest patients and in those with GCSE of very long duration, however, so in most cases a conclusion that the chance of survival is negligible is unwarranted.

4.2. Other Sequelae

Although survival is the outcome measure with the largest amount of data associated with it in published GCSE studies (due to ease of ascertainment), two other categories of neurologic sequelae are important for those who survive GCSE and can even come to dominate the clinical picture in these patients.

4.2.1. Epilepsy

The rate at which patients with an episode of SE will develop subsequent epilepsy varies widely among reports *(52)*. One study found that 40% of patients with an episode of SE developed subsequent epilepsy, about four times the rate following a single acute symptomatic seizure *(53)*. On the other hand, an older series found the rate of post-SE epilepsy to be 21% *(54)*, and another study that compared a prospectively gathered patient population to a retrospective group being followed in a neurology clinic found that the rates at which SE was followed by epilepsy were 25 and 72% in the two groups, respectively *(48)*. It is reasonable to conclude that the rate at which new epilepsy arises as a complication of SE is not firmly defined, but it may be higher than the rate following a single seizure. This supports the contention that prolonged seizures are more likely to lead to subsequent epilepsy than briefer ones, although an alternative explanation would be that patients who are already predisposed to developing epilepsy in the future may begin with more prolonged seizures at the onset. Even if one excludes those patients who have clinically ascertainable signs of a predisposition to epilepsy (e.g., idiopathic generalized EEG patterns), many patients with underlying epileptogenic processes that were "subclinical" prior to their episode of GCSE would not be definitively eliminated. The pathophysiologic mechanisms by which SE can lead to epileptogenesis, and how these might fit in with our current understanding of most epileptogenic processes *(55)*, are discussed elsewhere in this volume.

4.2.2. Cognitive and Other Neurologic Sequelae

The other major nonfatal category of GCSE sequelae involves neurologic deficits besides epilepsy, particularly cognitive or behavioral changes. It is difficult to find well-documented studies of post-GCSE cognitive changes in adult populations; most clinical studies of such post-GCSE effects are pediatric and retrospective. Comprehensive neurologic examinations and neuropsychologic evaluations both before and after SE are seldom available. Even when good documentation exists, a number of important variables affecting cognitive function are difficult to control, including the progression of any underlying neurologic disease that led to SE as well as the effect of anticonvulsant medications. One pediatric series found a low rate

(9%) of new neurologic deficits after SE *(48)*, in contrast with older studies reporting the development of mental retardation in 48% of post-SE children and other deficits in 37%; in the latter study 20% of these deficits were felt to be the result of the SE itself *(54)*.

The most informative adult study to date reported results of neuropsychologic testing on 143 adults with epilepsy, performed twice in each subject separated by a 5-yr interval *(56)*. Nine of these patients had SE during this interval. These patients worsened on testing, while control patients who did not have SE improved—but SE patients had lower IQ scores even before the episode of SE and were taking more anticonvulsants on average than controls. These findings lend support to the idea that cognitive worsening from GCSE may be more likely to occur in those with underlying intellectual disability or other neurologic dysfunction at baseline.

Over all, it appears that although some patients may develop new cognitive and other neurologic deficits following an episode of GCSE, the rate may be lower than previously thought and the proportion of these deficits that are clearly attributable to the GCSE itself rather than the underlying cause may be small. Clinicians should be aware that those with prior cognitive impairment may be most at risk.

4.2.3. Physical Injury

Although it is perhaps self-evident that an event as violent as an episode of GCSE can lead to physical injury, it would be ideal to understand the types and patterns of such injuries as well as their relative frequencies. This information would allow clinicians to look specifically for the common types of GCSE-associated injuries in patients who remain unable to communicate pain or discomfort after their GCSE episode, and might also allow, in particular cases, for a determination as to whether an injury is more likely to have resulted from the initial fall of a seizure or to the prolonged seizure activity itself.

Nevertheless, few descriptions exist of physical injuries specifically following SE. There is, however, a significant literature on injuries associated with isolated or recurrent GTC seizures, and it seems reasonable to assume that the nature of injuries would be the same in GCSE, albeit potentially more severe. Head injury appears to be the most common traumatic injury associated with seizures, occurring in 24% of patients who had had at least one seizure in the preceding year in one survey *(57)*, and accounting for half of the admissions for seizure-related injuries in another series *(58)*.

The most frequent orthopedic injuries described are proximal femur fractures, proximal humeral fractures, posterior dislocation fractures of the shoulder, and thoracic vertebral body compression fractures *(59)*. One survey found that 6% of patients who had had at least one seizure in the preceding year had suffered a fracture, with seizure severity, epilepsy duration, and drug-related adverse effects serving as the best predictors of developing a fracture *(57)*. Progressive scoliosis in disabled patients with frequent recurrent seizures has been well-described in the orthopedic literature *(60)*, and one case of scoliosis due to epilepsia partialis continua has been reported *(61)*.

Finally, burns, a well-known injury associated with seizures of many types, may be of particular relevance to GCSE because SE may increase the exposure time of patients to the responsible heat source and thus increase burn likelihood or severity. One survey of seizure clinic patients found that about 10% had had a seizure-related burn in their lives *(62)*.

5. MYOCLONIC STATUS EPILEPTICUS

Myoclonic SE, although generally considered to be a separate entity from GCSE, is discussed here because it is in fact generalized electrographically and is often thought of as "convulsive" because of its motor manifestations. Myoclonic SE can arise from a number of different causes, most commonly anoxic brain injury or toxic-metabolic encephalopathy *(63)*. Those with anoxia-related myoclonic SE have a poor course and prognosis: almost all are comatose, and the condition is nearly always fatal. When patients do survive, very few recover significant neurologic function *(63,64)*. In some cases GCSE may precede the appearance of myoclonic SE, leading some to postulate that the two conditions are closely related *(63)*. The poor prognosis attending the anoxia-related cases appears to be due to the underlying anoxic insult, rather to than the SE itself, so that the utility of aggressive treatment of myoclonic SE is unclear *(64)*.

Other causes of myoclonic SE include an underlying myoclonic epilepsy, such as a progressive myoclonus epilepsy syndrome *(65)*. Patients with juvenile myoclonic epilepsy can also develop SE, although frank myoclonus is not necessarily present as a clinical manifestation in these cases *(66)*. In such generalized epilepsy patients, an episode of myoclonic SE can be triggered by medication noncompliance or other acute epilepsy exacerbants, but the prognosis for return to baseline is better than in the anoxic cases *(67)*.

As discussed in Chapter 5, Section 3.1.1.4., the EEG during an episode of myoclonic SE can take on a number of different patterns and may help to identify the presence of an underlying generalized epilepsy syndrome *(67)*.

6. CONCLUSION

GCSE remains one of the most common and serious neurologic emergencies encountered by most physicians. Although usually approached with a treatment algorithm in mind, any case of GCSE requires that the treating physician make a serious attempt to identify the underlying etiology (potentially from a long list of possibilities), because this may significantly influence treatment and prognosis. In general, GCSE can arise in patients with earlier epilepsy, in those with acute neurologic insults, or in those with acute systemic insults. In some cases, GCSE represents the initial manifestation of an underlying seizure disorder.

Most outwardly visible clinical manifestations of GCSE are easy to recognize, but the convulsive motor activity tends to decrease in intensity and frequency with time, such that the late stages of GCSE may be characterized by only subtle signs and are more difficult to diagnose. In addition, a number of systemic physiologic

changes occurring during ongoing GCSE are important to recognize as well, although their origin is multifactorial and their influence on long-term prognosis unclear.

Mortality is high from GCSE but is dependent on a number of different factors, primarily etiology. Age and duration are also important to consider, although whether they play an independent predictive role is debatable. Other nonfatal sequelae of GCSE include the development of subsequent epilepsy, the appearance of cognitive and other neurologic deficits, and physical injuries. Our understanding of predictive factors for the development of these problems is generally lacking in most cases, although those with prior intellectual impairment may be at higher risk for cognitive worsening. The rates at which these sequelae develop (as well as the frequency with which they can clearly be attributed to the GCSE itself) are also not very well-defined.

Finally, myoclonic SE, which may be closely related to GCSE, most commonly arises in patients who have suffered anoxic-ischemic brain injury; in these cases prognosis is quite poor and the utility of aggressive treatment debatable. For patients with underlying myoclonic epilepsy syndromes, however, recovery may be complete.

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7
Focal Status Epilepticus

Donald L. Schomer

1. INTRODUCTION

Focal status epilepticus (FSE) is a condition in which there is an anatomically discrete, continuously discharging epileptic disturbance, lasting more than 1 h *(1)*, that is associated with a definable neurologic behavior. If that discrete and sustained discharge occurs in the temporal lobe or limbic region of the brain, the condition is referred to as nonconvulsive complex partial status epilepticus (discussed in Chapter 10). If the discharge is ongoing in systems that subserve language function, an aphasia may result (*see* Chapter 11). This chapter will deal with the disorders and conditions associated with FSE arising from other regions of the brain. This condition can be associated with a wide variety of neurologic disorders and have a multitude of signs and symptoms. These signs and symptoms vary according to the function of the brain area engaged by the discharge and can be as simple as a repetitive movement, as seen in epilepsia partialis continua (EPC), or as subtle as an inability to write to command (see case example).

2. DEFINITION OF TERMS

By definition, a sustained epileptic discharge in a discrete site in the brain is focal electrographic status epilepticus. This term, *focal electrographic status epilepticus*, is not one in general usage and its clinical significance is not known. Only if the patient is shown to be symptomatic can the physician conclude that the individual is in *clinical* focal status epilepticus. Motor signs can be seen and are recognized more easily than subtle changes in cognition or perception that must be demonstrated through elaborate testing. Therefore, most reported cases of FSE have been focal motor status epilepticus, and FSE has become almost synonymous with EPC.

The movements of EPC were recognized and described many years ago and are defined as "clonic muscular twitching repeated at fairly regular intervals in one part of the body for a period of days or weeks" *(1)* or "for a minimum of one hour, and recurring at intervals of no more than ten seconds" *(2)*. EPC is subdivided into two groups—type I and type II *(3)*. The distinction between the two lies in whether the pathology associated with the EPC is nonprogressive (type I) or progressive (type II).

From: *Current Clinical Neurology: Status Epilepticus: A Clinical Perspective*
Edited by: F. W. Drislane © Humana Press Inc., Totowa, NJ

In type I EPC (the classic pathologic example being Russian spring-summer encephalitis), the movements noted clinically tend to involve just one or several isolated muscle groups. Once these movements appear, they may spread outside of that discrete area and lead to complex partial or secondary generalized seizures, depending on the direction and degree of spread *(3,4)*. Type I EPC is usually associated with nonprogressive disorders, but if it occurs with a *newly acquired* nonprogressive lesion such as a stroke *and* with secondary generalized seizures, there is an overall grave prognosis for survival *(5)*.

Type II EPC is seen in the context of progressive central nervous system (CNS) abnormalities such as Rasmussen's encephalitis *(3)*. It is frequently associated with multiple seizure types and a greater variability of the muscle groups involved in the EPC *(3)*. Most commonly, simple partial and complex partial seizures coexist, but occasionally secondary generalized seizures are also reported *(6)*.

EPC may occur in the context of clinically significant metabolic disorders such as hyponatremia. In this case, there is often an earlier CNS lesion that provides the substrate for the EPC. If that lesion is nonprogressive, such as a stroke, the EPC is usually of type I and follows a more benign course *(5,7)*; if it is progressive, such as a glioma, the EPC is more likely to follow the type II pattern. The EPC that results from iatrogenic exposure to various medications or biologic agents such as metrizamide usually follows a course more typical of a type I disorder in that the movements are restricted to a few isolated muscle groups and are often self-limited *(8,9)*.

FSE not associated with EPC appears to be relatively rare and to follow a more benign course. Case reports of visual hallucinations due to FSE in areas confined to the visual cortex, or temporal association regions and surrounding parietal cortex, have been well-documented and make a case for the existence of FSE of nontemporal, nonfrontal, and nonlimbic origin *(10)*. Neuronal migration abnormalities and mitochondrial disorders appear to be the major predisposing conditions to the appearance of such FSE *(11,12)*. The clinical manifestations of FSE from these nonmotor and nontemporal lobe regions of the brain appear to depend on the function of the underlying brain.

3. ETIOLOGY AND EPIDEMIOLOGY

The disorders associated with FSE where EPC is the expression of the status epilepticus (the FSE-EPC complex) are the same major diseases associated with any partial seizure disorder, i.e., infectious, vascular, and neoplastic diseases. Primary brain disorders are less commonly associated with FSE-EPC. They include: focal atrophic lesions, traumatic brain injuries, isolated epileptic syndromes, mitochondrial disorders, and other primary neurologic developmental disorders. FSE-EPC may also be the presenting feature or a complication of a systemic metabolic disorder, the result of exposure to a medication such as cyclosporine, or caused by agents such as metrizamide used in diagnostic procedures that interact directly with the brain.

An infectious etiology for FSE-EPC is well-recognized. The first clinical descriptions of EPC are attributed to Kozhevnikov *(13)* and Bruns *(2)* and relate to a condition now known as Russian spring-summer encephalitis. This disorder is considered due to an infectious agent that primarily affects the peasant population of Siberia *(14)*, although isolated cases have been documented in eastern Europe and Scandanavia. It is a monophasic disorder that frequently leaves its victim with FSE-EPC. Tuberculosis was also a common infectious cause for FSE-EPC, as reported in early cases in the United States *(1)*. FSE-EPC occurs in association with AIDS *(15)* as an isolated abnormality or as a complication of recurrence of resistant tuberculosis and other opportunistic infections of the nervous system that are also associated with FSE-EPC on their own.

FSE-EPC is seen frequently in association with Rasmussen's encephalitis, a condition for which both infectious and autoimmune etiologies have been postulated *(6,16–20)*. FSE-EPC occurs in at least 50% of biopsy-proven cases of Rasmussen's encephalitis sometime during the course of the disease *(6)*. There are other cases of isolated FSE-EPC considered due to a viral encephalitis *(4,21)*. Importantly, it has not been attributed to acute bacterial meningitis or abscess in the English literature.

Vascular disease of the brain is associated with FSE-EPC *(2)* and includes cases of occlusive stroke, either old or recently acquired; embolic or hemorrhagic stroke; vascular malformation; vasculitis *(22)*; and congenital internal carotid artery hypoplasia *(23)*. FSE-EPC often coexists with a newly acquired vascular lesion and a systemic metabolic disturbance, most commonly hyponatremia *(5,7)*.

Progressive glial tumors are occasionally associated with FSE-EPC, as are astrocytomas, hemangiomas, lymphomas, metastatic tumors *(25),* and gliomatosis cerebri *(26)*. Although patients with FSE-EPC are frequently evaluated for brain tumors, their likelihood is, in fact, remote—not arising in 1690 cases of biopsy-proven frontal lobe tumors reported in one series *(25)*. It is so rare that it is worth reporting if EPC is the *first sign or symptom* of a primary brain tumor.

Other CNS disorders are occasionally associated with FSE-EPC. Brain trauma was related in one large study *(2)*. Several authors have reported a relationship to multiple sclerosis *(27,28)*. In one case of a possible relationship to Friedreich's ataxia *(29)*, there were several atypical features that raised the possibility of a misdiagnosis in a case of mitochondrial encephalopathy with lactic acidosis and strokes (MELAS) or mitochondrial encephalopathy with ragged red fibers (MERRF), conditions that seem to predispose to EPC *(30)*.

Nonketotic hyperglycemic diabetes mellitus has been associated with FSE-EPC in both children *(31)* and adults *(5,7)*. FSE-EPC can be the presenting feature of diabetes *(5)*, but more often it is seen as a consequence of long-term diabetes and coexists with an old or recently acquired CNS structural lesion. Hyponatremia associated with the nonketotic hyperglycemic diabetic state appears to be the critical metabolic derangement that predisposes to EPC. The presence of EPC is related to the severity of the hyponatremia in an almost linear fashion *(5)*. Other metabolic disturbances related to the occurrence of EPC include renal and hepatic encephalopathies.

Metrizamide *(8)*, penicillin, and azlocillin-cefotaxime *(9)* have each been suspected iatrogenic triggers for FSE-EPC.

There are very few data regarding the pathologic causes for FSE in parietal, occipital, and relatively silent areas of the brain. Dysplastic lesions and mitochondrial disorders are associated with FSE. Many clinicians are aware of these disorders because of other features in the clinical syndromes in their patients. Knowing that the disorder is present and that it predisposes to FSE, physicians are attuned to the possibility that sudden changes in behavior or cognitive function may be an expression of nonfrontal (nonmotor) FSE. It is possible, however, that many auditory or visual hallucinations or sudden loss of specific cognitive functions may have an epileptic origin but are never investigated and therefore never identified. The few well-described cases in the literature make for fascinating reading *(10,12)*.

4. CLINICAL DESCRIPTIONS

In FSE-EPC, the natural history and course reflect, for the most part, the underlying and predisposing disorder. Russian spring-summer encephalitis is a monophasic, nonprogressive disorder associated with a focal CNS lesion in motor-sensory cortex and EPC *(32)*. The EPC is usually unresponsive to medication. The best treatment for the EPC appears to be surgical removal of the affected cortical area, and dealing with the fixed motor-sensory deficits expected postoperatively *(14)*.

Rasmussen's encephalitis is almost exclusively a disorder of childhood, with a peak onset around 7 yr of age *(6,17)*. About half of biopsy-proven cases have an infectious or inflammatory disorder that precedes the onset of the seizures. Rarely is EPC the presenting seizure type, but it was seen eventually in more than half the cases in the Montreal Neurological Institute series *(6)*. If EPC is seen in a child with a history of other seizure types and progressive neurologic deficits, a presumptive diagnosis of Rasmussen's encephalitis can be made. The vast majority of cases studied thoroughly appeared to be restricted to one hemisphere *(6,16–18)*. It is usually slowly progressive over months or even years, but there are a few cases that appeared to arrest spontaneously. Rasmusssen's encephalitis may also play some role in more commonly recognized medically refractory complex partial epilepsy of temporal lobe origin *(33)*.

The best treatment of Rasmussen's encephalitis, like that of Russian spring-summer encephalitis, appears to be surgical *(6,34)*, but a more radical approach is used. If the patient has a complete unilateral visual field defect and a fixed hemiplegia, a modified hemispherectomy is the treatment of choice because it appears to control the seizure disorder completely, and little additional deficit is produced *(34)*. If successful, this procedure offers the best long-term outlook, both in terms of seizure control and for partial return of function. In addition to partial lobectomy, multiple subpial transection may be an alternative to hemispherectomy in patients who still have useful vision or useful motor function on the affected side *(35)*. Medications may help prevent secondary generalized seizures but typically have little effect on the EPC *(36)*.

In the original clinical studies from Boston City Hospital, where EPC was seen frequently in association with tuberculosis and cerebrovascular disease, the EPC itself was poorly responsive to medication and often associated with a fatal outcome. More recent studies show that when EPC (like periodic lateralized epileptiform discharges [PLEDs]) is associated with a stroke, there is often an acompanying metabolic abnormality *(5)*. The lesion may be newly acquired or chronic. The metabolic abnormality is most often hyponatremia, which may be associated with nonketotic hyperglycemic diabetes mellitus or related to altered salt-water metabolism due to the lesion, or worsened by the effect of seizures on the hypothalamus. If the hyponatremia is recognized early (prior to the appearance of coma) and treated aggressively along with the hyperglycemia, the prognosis is good. If the hyponatremia is recognized later (when the patient is already comatose), however, the outlook for survival is relatively grave *(5)*. In either situation, the stroke or other underlying disorder also plays a significant role in determining outcome. If the stroke is new, the prognosis also depends on its size and location and whether or not the brain has herniated. In the cases of tuberculosis or other treatable infections, the overall prognosis is related to the early diagnosis and treatment of the infection. No reports discuss the outcome of the related FSE-EPC itself.

In those few cases in which EPC was related to the use of the penicillins, azlocillin-cefotaxime, and metrizamide, it appeared to have a benign course. Exposure to the offending agents must be stopped and obvious seizure activity treated. Complex partial and secondary generalized seizures often respond to appropriate anticonvulsant treatment, but their continued, long-term use does not appear necessary *(8,9)*. The report on simple visual hallucinations probably related to FSE of the visual cortex does not provide sufficient information to draw conclusions about long-term treatment or outcome *(10)*.

In general, anticonvulsants help to prevent the spread of the FSE-EPC into complex partial or secondary generalized seizures, but rarely do they seem to alter the EPC significantly. In one noteworthy report, however, the calcium-channel blocker nimodipine was used with remarkable success in two patients with EPC *(37)*. The author speculated on its anticonvulsant properties as described by others *(38)*. Given its ability to block intrinsic neuronal bursting behavior, nimodipine should certainly be considered, but there have been no corroborative reports of its success in controlling EPC.

There are few reports of FSE occurring in nontemporolimbic and nonmotor systems. Two reasons may account for this observation. It may be that FSE-EPC occurs rarely in those networks, or perhaps, as with the FSE-EPC that *is* recognized, it occurs in relatively small neuronal generators seen poorly on scalp electroencephalography. Its recognition depends on the clinical manifestation of brain activity in the area affected by the FSE, e.g., with aphasia, alexia, or agraphia. If part of FSE, these symptoms should be sudden or intermittently recurrent. Sensory, autonomic, endocrinologic, or attentional alterations could also result from such sustained discharges if they occur in appropriate brain regions. Discrete focal

electrographic status epilepticus may not be as rare or unusual a phenomenon as the literature suggests but simply difficult to recognize (*see* case example in Section 6).

5. ELECTROPHYSIOLOGIC AND RADIOLOGIC STUDIES

EPC is felt to represent an irregular focal epileptic discharge of cortical origin *(39–41)*. Early writers in the field were disturbed by the lack of consistent coherence between scalp-recorded discharges and the myoclonic jerks recorded from affected muscle groups *(1,2)*. Several pointed out that some patients seemed to have no clear scalp discharge, but when they came to electrocorticographic investigations the same patients had very discrete areas where repetitive discharges were seen though they had not been recognized on the standard EEG.

The physiology of the cortical generators for these discharges is fairly well established *(4)*. Several neurophysiologists have found a unilateral enhancement of the somatosensory evoked potential associated with EPC *(4,39,41)*. This is similar to earlier observations in patients with myoclonic epilepsy *(42)*. In addition, there is a transcortical long loop reflex in the brain area subserving the arm that is distinctly abnormal and suggests a facilitation of these reflex activities *(40,43)*. These findings have been verified in further studies *(4)*.

One useful technique records multichannel EEG activity with an averaging procedure triggered from a muscle jerk *(4,42)*. This technique, called *back-averaging,* allows the investigator to record, see, and measure averaged EEG events that preceded the jerk. Researchers found that a cortical epileptic event was seen consistently prior to the peripheral myoclonic jerk, with an appropriate latency suggesting that this cortically generated event was transmitted via the corticospinal tract *(4)*. They also found that the somatosensory evoked potential from the affected limb is enhanced and has an altered latency of cortical onset, as well as a different morphology from the back-averaged spike discharge. In addition, there was a parietal subcortical lesion in one extremely well-studied patient *(4)*. The authors concluded that this patient had position-enhanced myoclonus originating from the contralateral motor cortex, due to enhanced cortical-cortical connections from the sensory cortex to the motor cortex. This excitatory state existed because the sensory cortex supported an enhanced evoked response due to the underlying lesion which partially deafferented that cortex. In addition, the motor cortex produced spontaneous epileptic discharges associated with peripheral myoclonic jerks. The motor cortex was possibly in a state capable of producing spontaneous discharges because it was partially disinhibited by the sensory cortex connections.

There is little doubt that there is a cortical origin of the myoclonic jerks enhanced by joint position, but they are evoked rather than spontaneous. This suggests that many cases with subcortical lesions associated with FSE-EPC have a common denominator of enhanced focal cortical excitability mediated by partial undercutting (and therefore partial deafferentation) of the neocortex connected to or dependent on

the site of the lesion *(1,2,25,44,45)*. This mechanism accounts for diminished local inhibition and thus enhanced excitability.

The EEG can aid the diagnosis and evaluation of patients with FSE-EPC and has utility in evaluating coexistent underlying diseases. In Rasmussen's encephalitis the EEG often shows significant lateralized slow wave activity and may give evidence for other seizure types or projected abnormalities suggestive of widespread but lateralized disease *(46)*. Lateralized asymmetric background slowing is noted frequently. Similar findings are often noted when the underlying disturbance is a high-grade glial tumor, but epileptic features are observed less frequently. In cases of focal nonprogressive lesions such as old subcortical strokes, the background is rarely asymmetric and, in fact, is usually normal. This point may help in differentiating such disorders from structural disease with coexistent metabolic disorders—where the metabolic encephalopathy is independently associated with a diffusely abnormal background. That the onset of FSE-EPC is also associated with PLEDs is not surprising because there are many overlapping clinical features of the two disorders *(24)*.

The radiologic imaging evaluation of patients with FSE-EPC is changing rapidly. Computed tomography (CT), magnetic resonance imaging (MRI), and cerebral angiography have been used for many years and are effective when looking for focal structural abnormalities and progressive disorders *(47)*. Their use in determining a prognosis is as well recognized in FSE-EPC as it is in the evaluation of partial epilepsy in general. High resolution MRI with fluid attenuated inversion-recovery (FLAIR) sequences is the best technique to visualize some of the microdysplastic lesions that may predispose to FSE when standard MRI fails to show discrete abnormalities *(48)*. This is also true for the cortically restricted abnormalities seen in mitochondrial diseases. Dynamic imaging with positron emission tomography (PET) and single photon emission computed tomography (SPECT) is emerging as a useful tool in the evaluation of the metabolic effects of FSE-EPC, especially when CT and MRI are normal *(4,49,50)*. These two techniques, particularly PET, may also be helpful in furthering our understanding, in an indirect way, of the biochemical and metabolic features associated with the abnormal physiology.

6. CASE EXAMPLE OF FOCAL STATUS EPILEPTICUS WITHOUT EPC

A middle-aged man was recovering from a lung transplant necessitated by progressive shortness of breath from obstructive lung disease *(51)*. Postoperatively, he had a generalized convulsion and was referred to the EEG lab because his family felt that he was not back to his normal mental state. On EEG, he had recurrent and prolonged epileptic discharges originating from the left parietal-parasagittal occipital region (Fig. 1). The clinical seizure he had had earlier was then thought to have been secondarily generalized, and he was treated with loading doses of anticonvulsants. Nevertheless, he continued to have frequent prolonged electrographic seizures interrupted by PLEDs (Fig. 2).

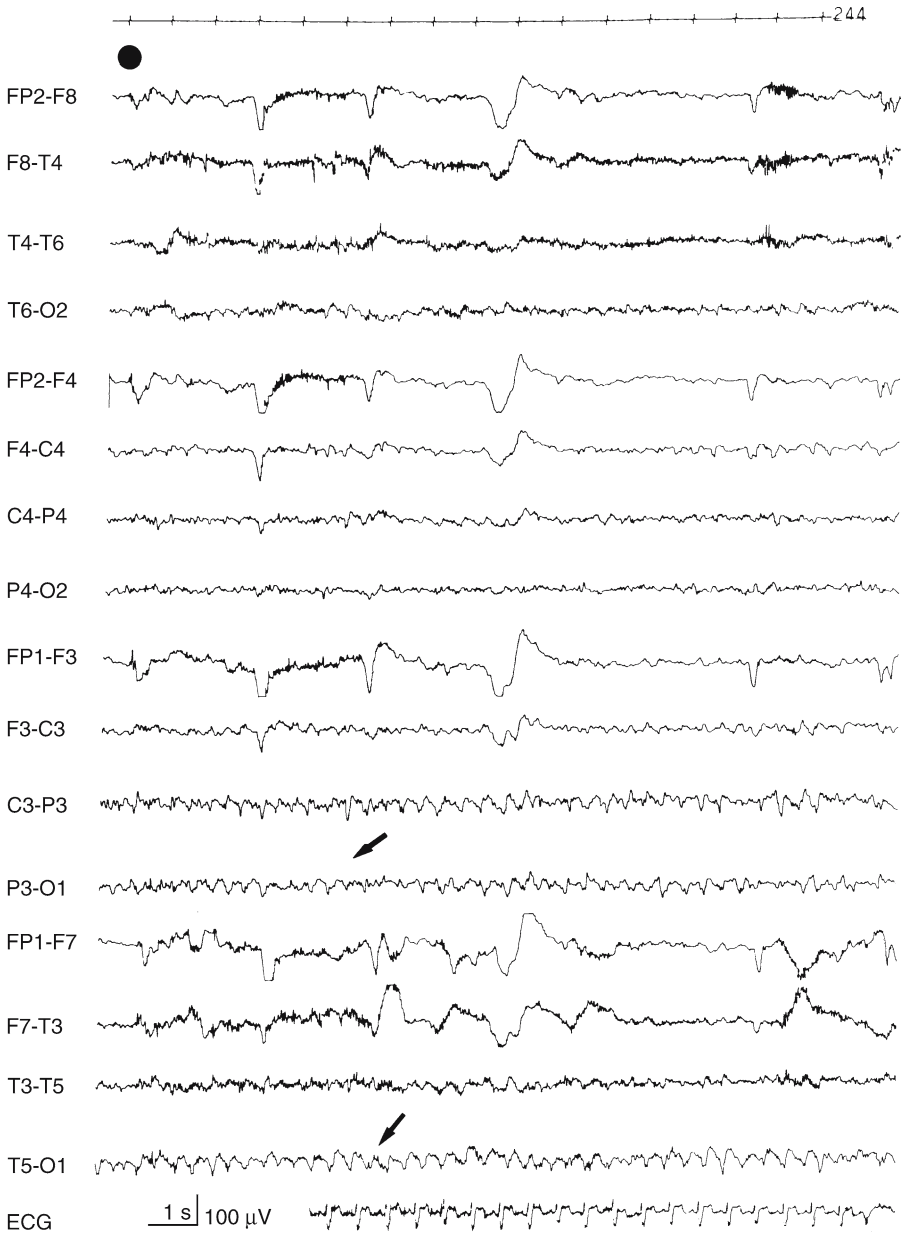

Fig. 1. This EEG was performed during the time when the patient was demonstrated to be symptomatic with "agraphia." The arrows demonstrate the presence of sustained epileptic activity maximum at the P3 and O1 sites, which correspond to the left parietal-parasagittal occipital area.

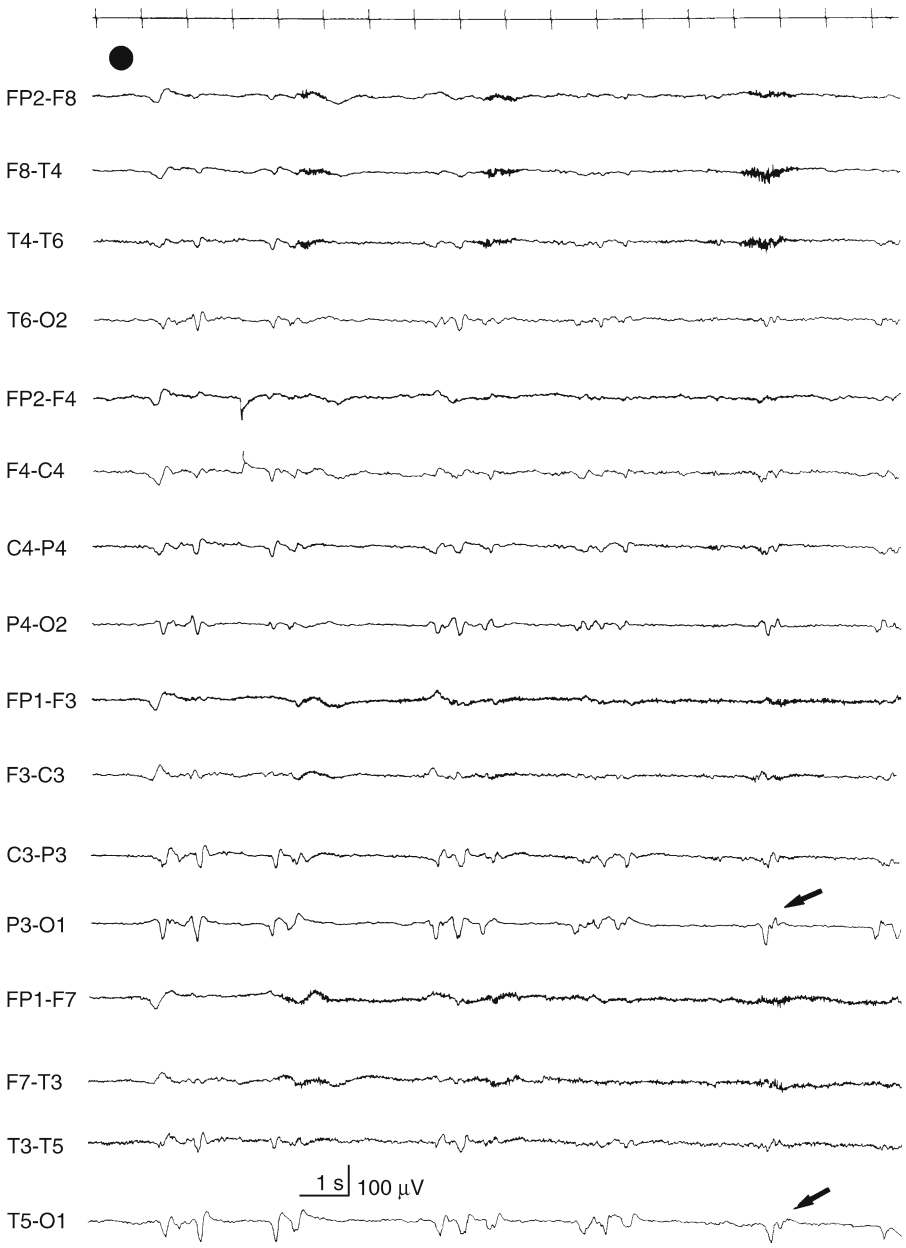

Fig. 2. This EEG was obtained later when the patient was no longer symptomatic with "agraphia." It demonstrates PLEDs, maximum broadly over the left posterior quadrant and identified by the arrows. This abnormality was later replaced by a normal background, which developed several days after the symptoms cleared.

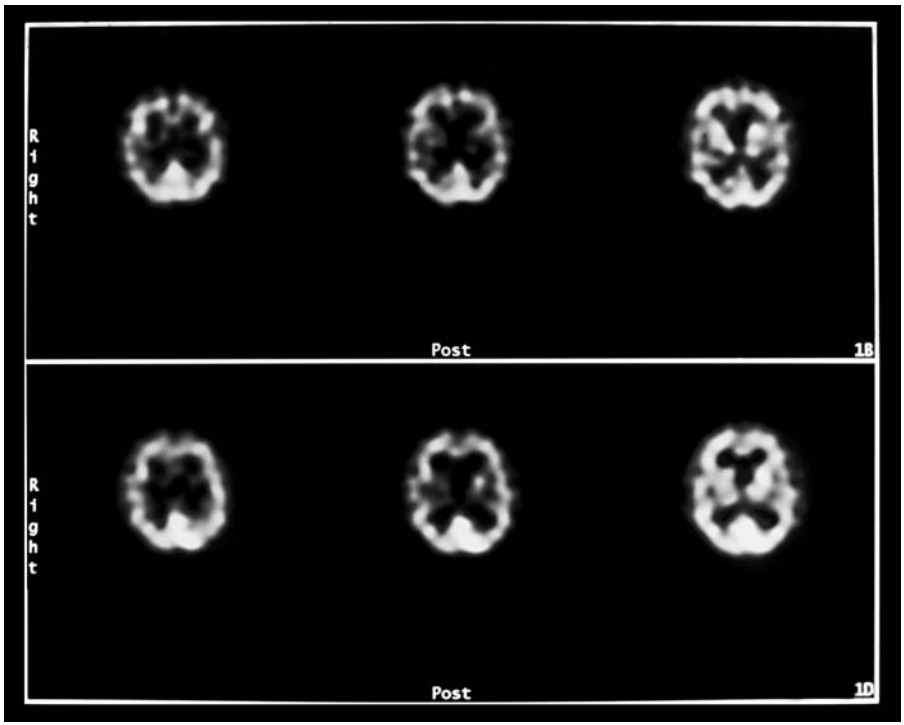

Fig. 3. The pictures on this SPECT scan were obtained at two different times and displayed one on top of the other to demonstrate the differences between the two states. The bottom series was done while the patient was symptomatic. They show a large area of increased blood flow posteriorly and to the left. The top three scans are matched for areas and were obtained after successful resolution of symptoms. This was interpreted as normal but significantly changed.

An MRI scan was interpreted as normal. The patient had an "ictal" SPECT that demonstrated a profound high flow abnormality in the same area as the EEG abnormality (Fig. 3, lower pictures). The SPECT abnormality resolved several days later when the EEG discharges stopped (Fig. 3, upper pictures).

The patient underwent extensive neurologic and neuropsychologic testing when the EEG showed the epileptic abnormality; testing was repeated after the electrographic status had resolved (findings summarized in Table 1). The principle finding was his inability to write to command while the discharges were present (Fig. 4). He was able to write only two letters (one word) (Fig. 4, area 1) while the EEG demonstrated the continuous epileptic activity. When that activity ceased and was replaced by the PLEDs, he was able to write to command (Fig. 4, area 2) with a few spelling errors (Fig. 4, sites a, b, and c).

This example of "ictal agraphia" occurs in the context of a neuroanatomic understanding of the various components of writing (illustrated in Fig. 5). The location of

Table 1
Neuropsychologic Testing for Case Report

	Interictal	Ictal
Writing to dictation	+++ (slow iteration of letters; spelling mistakes compatible with level of education	0 (dramatically reduced, *see* text)
Naming	++++	++++
Repetition	++++	++++
Oral comprehension	++++	++++
Reading aloud	+++ slow and deliberate	++ slower than interictally
Spontaneous speech	++++	++++
Spelling (orally)	+++ possible for simple words	++ slight increase in spelling errors
Written comprehension	++ moderately impaired	N/A not tested
Ideational and ideomotor praxis	++++	N/A not tested
Constructional praxis	0 apraxia	N/A not tested
Visual gnosis (color, line drawings, superimposed figures -Poppelreuter-)	++++	N/A not tested
Digital gnosis	+++ frequent errors between middle and ring finger of both hands	+++ unchanged
Written calculation	++ impaired	N/A not tested
Oral calculation	+++ possible for simple arithmetic	N/A not tested
Trail-Making Test (A and B)	+ impaired	N/A not tested
Luria's alternating figures	++ tendency to perseverate	+ increased tendency to perseverate
Word fluency	++++ 17 animals in 1 min	++ reduced (8 animals in 1 min)
Verbal span numbers forward numbers backward	+++ 5 3	++ 4 N/A – not tested

0 = severe impairment, + = marked impairment, ++ = moderate impairment, +++ = mild impairment, ++++ = normal.

This table outlines the various studies performed on this patient, the times when they were done (ictal vs interictal), and the graded results. Not all possible tests were administered nor were all of those administered able to be repeated due to the transient nature of the symptoms and the need to treat aggressively.

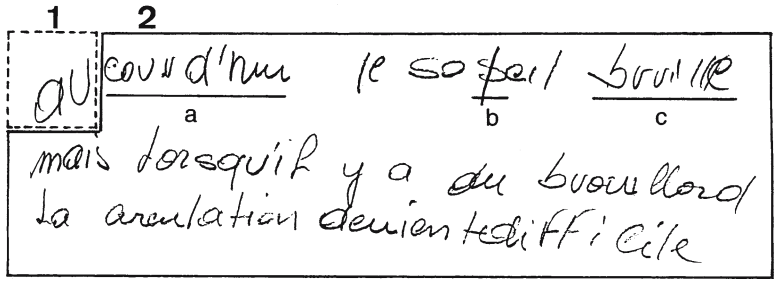

Fig. 4. This patient's main neuropsychologic abnormality is shown here. The subject was repetitively given this statement orally and asked to write what he heard. During the time that his EEG showed the abnormality in Fig. 1, he was able to write only that which is seen in the box labeled no. 1. When the EEG showed the activity in Fig. 2, he was able to produce rapidly the writing seen in the second box. It demonstrated a few spelling errors that are common in mildly confused patients (letters a, b, c). He expressed frustration during the task while the EEG showed the focal status discharges, complaining that he knew what he needed to do but could not figure how to get the letters to come out.

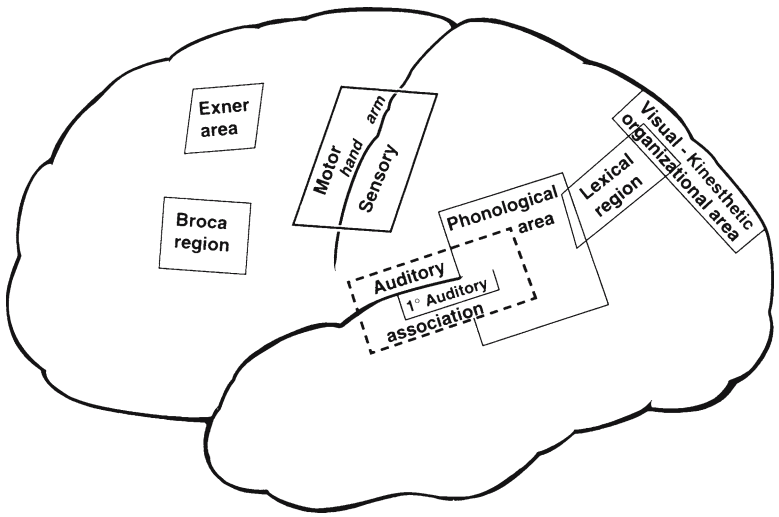

Fig. 5. This left hemisphere diagram shows the areas directly involved in writing in a normal right-handed individual. The area called the visual-kinesthetic organizational area is the area involved with seizure activity in this patient.

this FSE was in the visual-kinesthetic organizational area, located in the left posterior parietal-parasagittal occipital area of the brain. Based on the stroke literature, this area appears to support a function similar to that which was lost transiently in this case with seizures *(52,53)*.

This patient was also toxic on cyclosporine. The dosage was reduced and he was able to be withdrawn from his anticonvulsants ultimately, without recurrence of seizures. This case illustrates an example of nonmotoric focal status epilepticus in which the deficit, related to focal seizure activity, was difficult to demonstrate. When demonstrated, however, it was remarkably well related to known neuroanatomic functional-pathologic studies. It also shows that such cases exist without an identifiable structural abnormality and can be iatrogenic.

7. SUMMARY

Focal status epilepticus that is not related to the temporal lobe or limbic system and unrelated to speech is most commonly associated with epilepsia partialis continua. There are two types of EPC—directly related to whether or not the underlying pathology is progressive. The classic type I form is relatively simple in its expression and was originally described in the benign condition called Russian spring-summer encephalitis. Type II, seen most frequently in the progressive disorder called Rasmussen's encephalitis, has variable muscle groups involved and is often associated with multiple seizure types. The outcome of EPC is more often related to the underlying disorder than to the presence of the EPC itself. Anticonvulsants are better at controlling the complex partial or secondary generalized seizures than they are at controlling the EPC. Cases of FSE involving the parietal and occipital lobes of the brain are underreported, perhaps because they occur infrequently or possibly because they remain unrecognized due to the lack of an obvious clinical accompaniment.

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III Basic Considerations

8

Cellular Physiology of Status Epilepticus

Omotola Hope and Hal Blumenfeld

1. INTRODUCTION

Status epilepticus (SE) is one of the most physiologically extreme conditions encountered in the nervous system. Neurons fire at very high rates, releasing massive amounts of neurotransmitter and neuromodulatory molecules. Dramatic changes occur in membrane potentials and ionic distributions. There are marked increases in metabolic energy demands for glucose and oxygen, and in cerebral blood flow. Ultimately, during SE, a sequence of reversible and irreversible changes occurs at the level of single cells, as well as at the level of systemic physiology.

What are the cellular biochemical, neurotransmitter, and electrophysiologic mechanisms that promote the transition from normal neuronal activity to status epilepticus? Once SE is initiated, what are the mechanisms responsible for maintaining it, and what mechanisms finally lead to its termination? The complete answers to these questions remain unknown, but recent investigations carried out at multiple levels have shed new light on the mechanisms of initiation and maintenance of status epilepticus. Although several forms of SE exist (*see* Chapter 2), the vast majority of research has been done on generalized tonic-clonic SE, the focus of this chapter. Lessons learned from generalized tonic-clonic SE may have some applications for improved understanding of other forms of SE as well.

We will begin by reviewing several model systems in which the cellular physiology of SE can be studied. Next, we will discuss the stages of status epilepticus and how they relate to events at the cellular and molecular levels in initiation, maintenance, and termination of SE. (Pathologic changes and mechanisms of cell injury in SE are reviewed in Chapter 9.) Finally, we mention possible clinical applications of this work and future directions in which further studies are needed.

2. MODELS FOR INVESTIGATING CELLULAR PHYSIOLOGY OF STATUS EPILEPTICUS

Human studies have yielded crucial information about the clinical, electroencephalographic, and systemic physiologic events that occur during generalized tonic-clonic status epilepticus *(1)*. Nevertheless, the ability to investigate mechanisms of SE

From: *Current Clinical Neurology: Status Epilepticus: A Clinical Perspective*
Edited by: F. W. Drislane © Humana Press Inc., Totowa, NJ

at the cellular level in humans is clearly limited and, therefore, most studies have been done in animal experimental models. Repeated tonic-clonic seizures resembling human SE can be induced both in intact animals and in in vitro brain-slice preparations. Different brain regions show variable susceptibility to induction of seizures and SE. For reasons that are not fully understood, limbic structures tend to be the most seizure-prone in both in vivo and in vitro preparations. Therefore, many studies have focused on SE induced in limbic and paralimbic structures such as the hippocampus, entorhinal cortex, and amygdala, although SE can be induced in nonlimbic regions as well.

Brain-slice preparations, particularly those including the rodent hippocampus and entorhinal cortex, can be induced to generate repeated epileptic discharges resembling tonic-clonic status epilepticus through several different experimental manipulations. These manipulations include elevated extracellular potassium *(2)*, decreased extracellular magnesium *(3)*, decreased extracellular calcium *(4,5)*, and administration of the potassium channel blocker 4-aminopyridine (4AP) *(6)*. Advantages of in vitro preparations are the ability to introduce pharmacologic and ionic changes in the extracellular environment relatively easily and ready access to intracellular recordings of single neurons. In vitro models, however, consist of a much more limited network than exists in an intact animal and, therefore, may not replicate fully the conditions encountered during SE clinically. For this reason, many investigations have been done with in vivo experimental models.

The major in vivo models of SE can be divided into chemical methods and electrogenic methods, as summarized by Fountain and Lothman *(7)* (*see* Table 1). In chemical methods, various compounds are applied, either systemically, directly to the brain parenchyma, or into the ventricular system. Although the rat has been the most frequently studied model, the mouse, rabbit, piglet, baboon, and other species have been used. Chemicals can be divided into promoters of excitatory neurotransmission (e.g., kainic acid, domoic acid) and those that oppose inhibitory neurotransmission (e.g., bicuculline, penicillin).

The kainic acid model is one example of a widely used chemical method of inducing status epilepticus *(8)*. Kainic acid is a powerful glutamatergic agonist with excitotoxic properties. By varying the dose and the route, limbic seizures with various degrees of generalization can be produced. The lithium-pilocarpine model of SE has also been used extensively. Animals are pretreated with lithium chloride, and then given pilocarpine, a muscarinic agonist that produces repeated generalized tonic-clonic seizures *(9)*. Although chemical models of status epilepticus are relatively easy to create and study, the nature of this type of model makes it difficult to distinguish between effects caused by SE and direct neurotoxic effects of a particular drug.

Electrogenic methods of studying SE partially avoid this problem because SE persists in these models even after the electrical stimulus has terminated, although direct effects of the electrical stimulus itself must still be considered. Electrogenic seizures produced by repeated stimulation were originally demonstrated by Goddard in the kindling model *(10)*, and it was subsequently found that prolonged

Table 1
Animal Models of Status Epilepticus

I. Chemical Methods[a]	**II. Electrogenic methods**
A. Systemic or intracerebroventricular administration	**A. Sites of stimulation**[d]
NMDA (mouse)[b]	Amygdala
Quisqualate (mouse)[b]	Hippocampus
Kainic acid[b]	Piriform cortex
Domoic acid[b]	Olfactory cortex
Pentylenetetrazol (rabbit, piglet, mouse)[c]	Caudate/putamen
Bicuculline (piglet, baboon, sheep)[c]	Perforant path
Allylglycine[c]	
Pilocarpine ± lithium	**B. Electrical stimulus**
Soman (guinea pig)	Prolonged intermittent: perforant path stimulation for 24 h[e]
Flurothyl	Rapidly recurring: 20 Hz stimulation × 20 s every min for 180 min[f]
B. Intracerebral administration	Continuous: 50–70 Hz stimulation × 9 min, every 10 min, for 90 min[g]
Kainic acid into amygdala (cat)	
Dibutyl cAMP into amygdala	
Folic acid into cortex	
Penicillin into cortex	
Bicuculline into cortex	
Picrotoxin into cortex	
Cobalt lesion + homocysteine	

NMDA= *N*-methyl-D-aspartate; cAMP= cyclic adenosine monophosphate.
Reproduced from ref. *7* with permission.
[a]All methods have been used in rats; other species used recently are in parentheses.
[b]Compounds that promote excitatory neurotransmission.
[c]Compounds that oppose inhibitory neurotransmission.
[d]*(53).*
[e]*(54).*
[f]*(55).*
[g]*(13).*

stimulation can result in spontaneous seizures and self-sustaining SE *(11–13)*. Many sites and variations in stimulus parameters have been used, as summarized in Table 1. For example, Lothman and colleagues stimulated the hippocampus via a depth electrode with 50-Hz trains for 9 min with a 1-min break for EEG observation with repeated 10-min blocks for 30 to 60 min or until self-sustained SE occurred *(13)*.

3. STAGES OF STATUS EPILEPTICUS

Since the earliest clinical descriptions in the 1800s *(14–16)*, it has been recognized that status epilepticus evolves through several stages with distinct behavioral and physiologic changes occurring at different times after onset. Before treatments were available, it was observed that SE is typically heralded by discrete individual

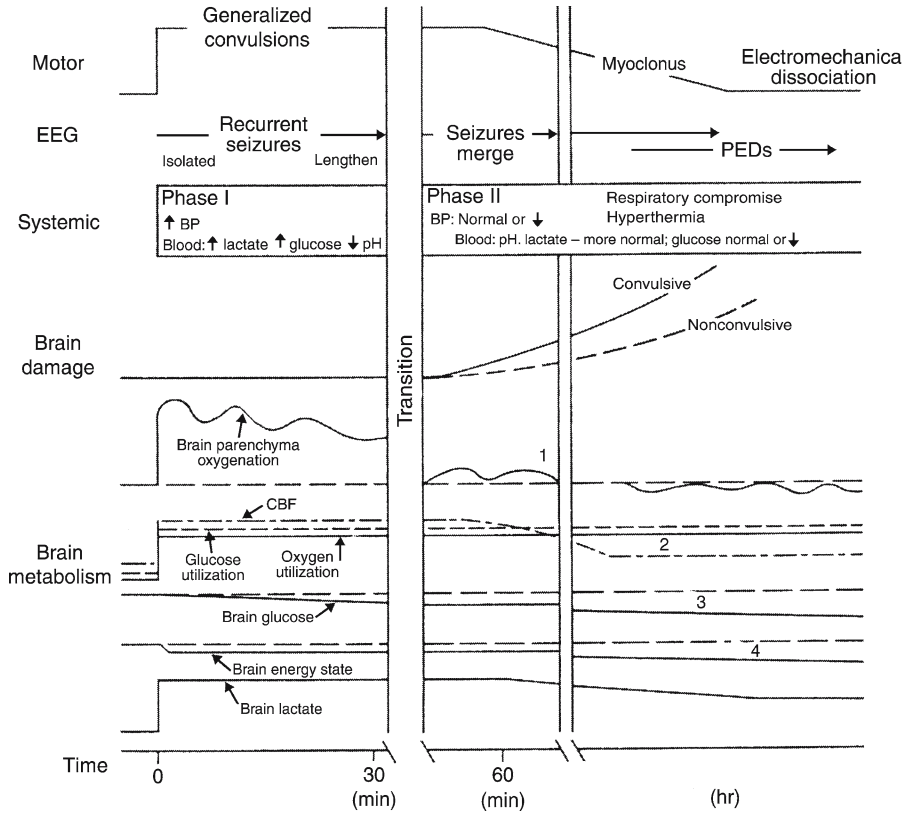

Fig. 1. Summary of systemic and brain physiological changes during different stages of status epilepticus. A transition occurs between 30 and 60 min after onset, in which compensatory mechanisms fail, leading to sustained status epilepticus and cerebral injury. PEDs, periodic epileptiform discharges; CBF, cerebral blood flow. (Reproduced from ref. *1* with permission.)

seizures that become more frequent, and eventually merge into repeated seizures without recovery of consciousness *(14,17–19)*. This initial "convulsive phase" is later followed by a "meningitic" or "stuporous phase" in which motor convulsions become more subtle or nearly absent, coma persists, and a variety of autonomic changes occur, including an inevitable rise in temperature, whether or not infection is present. These early observations have largely been confirmed by subsequent clinical and experimental studies of the systemic and brain physiologic changes during the course of SE *(1,20)* (*see* Fig. 1). Studies from many models demonstrate an early phase of status epilepticus, which we refer to here as "initiation," in which discrete seizures occur and merge gradually. A crucial transition next occurs, after about 30 to 60 min, to the "maintenance" phase, in which motor convulsions fade, but abnormal electrographic seizure activity continues, and multiple compensatory systems

fail, resulting in refractory seizures (unresponsive to many medications) and brain damage. As discussed in the sections that follow, a variety of neurotransmitter and neuropeptide changes occur that may account in part for this transition. Experimental work demonstrating some of the more global changes is depicted in Fig. 1.

During SE, a variety of parameters, including blood pressure, heart rate, pH, brain oxygenation, and glucose levels change in a predictable way and likely contribute to neuronal injury. Meldrum and colleagues made important contributions to undstanding the role of systemic physiologic changes when they induced SE in baboons with intravenous injections of bicuculline *(21,22)*. As seen in the third line of Fig. 1, they found two systemic stages of SE. In the first 25 min, blood pressure increased with each seizure, and serum glucose and acidemia increased. In the second phase, there seemed to be an inability to compensate, and blood pressure was less reactive; blood chemistries normalized and then worsened. Paralysis and artificial ventilation did not fully protect neurons from damage *(23)*.

Measures of brain metabolism have demonstrated increased glucose and oxygen utilization throughout SE, while at least some studies have found a late decrease in cerebral blood flow, suggesting a possible mismatch between metabolic demands and delivery late in SE *(24)* (Fig. 1). Using microelectrodes to measure oxygen tension in cerebral tissue, it was shown that oxygen tension rose and fell with each separate seizure until 30 to 40 min of seizures, at which point oxygen tension was less reactive, again suggesting a mismatch between metabolic demands and substrate delivery late in SE *(25)*.

Trieman has shown that some human seizures and animal experimental models progress through a series of five typical electroencephalographic stages during the course of SE *(26)* (Fig. 1, second line):

1. Discrete electrographic seizures.
2. Merging of electrographic seizures (waxing and waning of ictal discharges).
3. Continuous ictal discharges.
4. Continuous ictal discharges punctuated by flat periods.
5. Periodic epileptiform discharges on a relatively flat background.

These findings again suggest that a crucial transition occurs relatively early during SE, associated with the merging of electrographic seizures, that results in a variety of physiologic changes that may lead to sustained seizures and brain damage. As discussed in the following sections, studies of GABAergic and glutamatergic neurotransmission, and those of neuropeptides, support this model and have begun to provide some mechanistic understanding of this transition at the level of cellular physiology.

4. SEIZURE INITIATION AND INITIATION OF STATUS EPILEPTICUS

The mechanisms that initiate individual seizures in status epilepticus are likely similar to mechanisms initiating a single seizure. Local changes in the balance

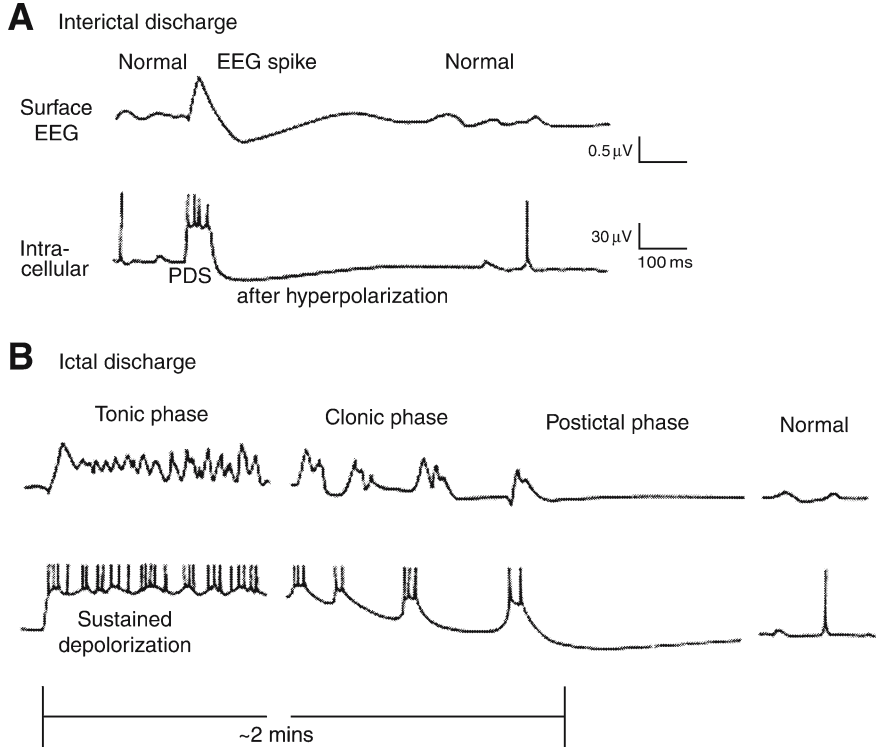

Fig. 2. Neuronal and EEG correlates of epileptiform discharges. **(A)** Interictal spike on surface EEG corresponds with a single paroxysmal depolarizing shift (PDS) whereas in **(B)** a sustained depolarization correlates with a single seizure lasting approx 2 min. (Reproduced from ref. *27* with permission.)

between inhibitory and excitatory influences result in a paroxysmal depolarizing shift (PDS) that corresponds to an interictal spike on EEG (Fig. 2). Usually, surround inhibition limits the spatial extent of the interical spike *(27,28)*, but with a large enough excitatory impulse there can be spread either locally or via excitatory pathways, causing a sustained depolarization (Fig. 2B). Several in vitro models of seizures using hippocampal slices in different media including low calcium (Ca^{2+}), zero magnesium (Mg^{2+}), or elevated potassium (K^+) suggest that many local factors can influence seizure initiation (reviewed in ref. *29*) (Fig. 3). For example, elevations in extracellular K^+ can produce a positive shift in membrane potential, causing it to be closer to the action potential threshold. This positive shift reduces the K^+ efflux at a given potential which can then lower $GABA_B$-mediated inhibitory postsynaptic potentials (IPSPs) and reduce the amplitude of K-mediated burst after hyperpolarization. Local changes in extracellular K^+ can also relieve the

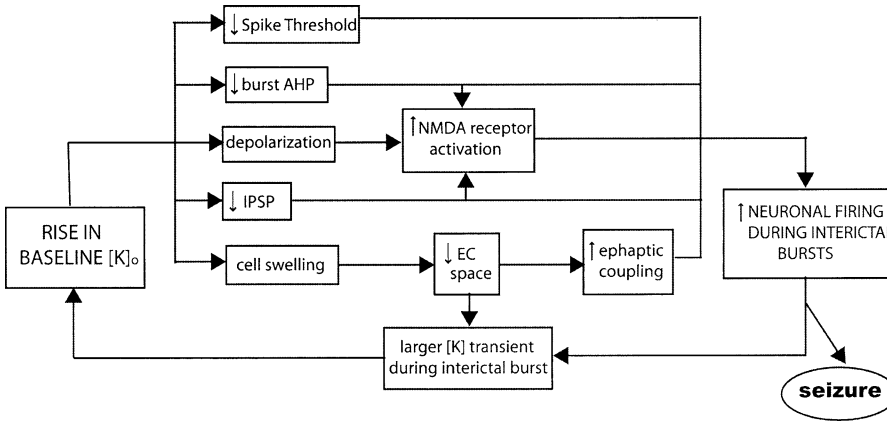

Fig. 3. Schematic representation of mechanisms initiating seizures in hippocampal neurons, emphasizing the role of elevated extracellular potassium *(2,29)*. Local factors, such as a rise in extracellular potassium (K_o), can initiate a seizure. Artificially imposed elevation of K has multiple consequences, including a decrease in spike threshold, decrease in afterhyperpolarization (AHP), depolarization, decreased inhibitory postsynaptic potentials (IPSP), and cell swelling, all of which work to increase the number of pyramidal cells firing in CA1 of the hippocampus in response to the interictal bursts of CA3 cells. The increased firing leads to further increases in extracellular potassium, and this cyclic process continues until the threshold for a seizure is reached. NMDA = *N*-methyl-D-aspartate; EC = extracellular. (Reproduced from ref. *2* and *29* with permission.)

voltage-dependent *N*-methyl-D-aspiritate (NMDA) receptor blockade by Mg^{2+}. Relieving magnesium blockade can activate the more potent NMDA-mediated excitatory cascade. All these factors, and others, can lead to an increased chance of interictal burst firing producing a seizure (Fig. 3).

The evolution of single seizures to status epilepticus may depend on the intensity of the precipitant *(20)*. For example, in experimental electrogenic SE, it usually requires at least 30 min of stimulation to produce self-sustained SE *(7)*. Initially, usually up until about 30 min of stimulation, seizures are stimulus-bound, i.e., the seizures continue only for as long as stimulation is occurring. As stimulation continues, however, self-sustained SE ensues, i.e., there are repetitive seizures without continued stimulation. Similarly, the same chemical convulsant agents that produce single seizures may produce SE when given at higher doses.

As discussed, SE appears to consist of an initiation stage during which single seizures gradually coalesce, followed by a transition to a second stage in which multiple physiologic changes occur and seizures become more sustained and refractory to medical therapies. As summarized in Table 2, many possible mechanisms contribute to the initiation phase of SE, and these can be blocked by many agents.

Table 2
Summary of Mechanisms That Affect the Initiation and Maintenance of Status Epilepticus

Initiators	Blockers of initiation phase	Blockers of maintenance phase
Low Na_o^+, High K_o^+	Na^+ channel blockers	
$GABA_A$ antagonists	$GABA_A$ agonists	
Glutamate agonists: NMDA, AMPA, kainate, low Mg_o^{2+}, low Ca_o^{2+} stimulation of glutamatergic pathways	NMDA antagonists, high Mg_o^{2+} AMPA/kainate antagonists	NMDA antagonists
Cholinergie muscarinic agonists, stimulation of muscarinic pathways	Cholinergic muscarinic antagonists	
Tachykinins (SP, NKB)	SP, neurokinin B antagonists	SP antagonists
Galanin antagonists	Galanin agonists	Galanin
Opiate δ agonists	Opiate δ antagonists	
Opiate κ antagonists	Dynorphin (κ agonist) Somatostatin NPY	Dynorphin

NKB, neurokinin B; SP, substance P; NPY, neuropeptide Y.
(Reprinted from ref. *49* with permission.)

During the maintenance phase, many agents may suppress SE transiently, but permanent blockade is more difficult to achieve. The sections that follow detail several neurotransmitter and neuromodulatory systems that, based largely on work in animal models, are proposed to contribute to initiation and maintenance of SE. First, however, anatomic networks commonly involved in SE in these models are reviewed briefly.

4.1. Anatomic Networks in Status Epilepticus

The spread of seizure activity is dependent on normal cortical and subcortical networks or circuits. The most studied network is arguably the limbic system, of which the hippocampus is an important structure. Historically, there is a very strong correlation between hippocampal anatomy and chronic epilepsy. Perhaps this is why it is the most widely studied area for SE. Is the hippocampus a critical relay point for seizures? Is it the actual source of seizures? These kinds of questions have not and possibly cannot be answered completely, but the limbic system is clearly at increased risk for injury during SE and, due to its nature and connections with the rest of the brain, it may play a crucial role in generating seizures *(27)*. Autoradiography studies in the rat lithium-pilocarpine model show a progression of anatomic involvement from limbic olfactory areas, to widespread cortical regions *(30)* (Fig. 4). It has been hypothesized that within the limbic

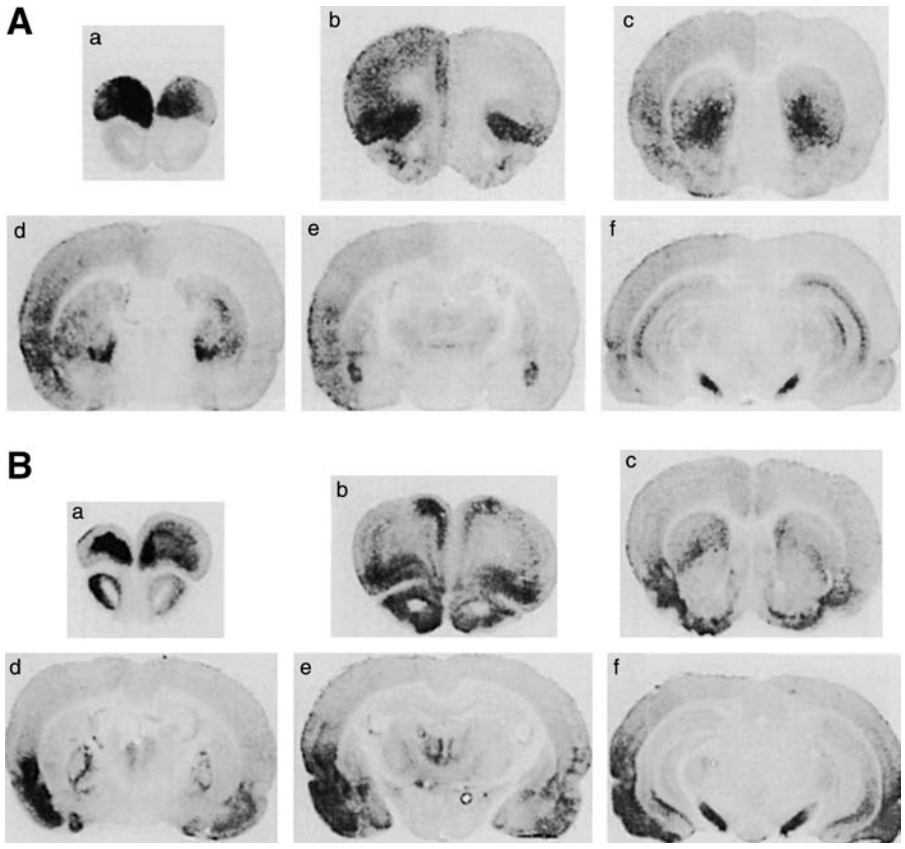

Fig. 4. Functional mapping of status epilepticus using ^{14}C-2-deoxyglucose (2DG) autoradiography *(30)*. Rats received lithium chloride followed by pilocarpine to produce SE. The first study was done at 10 min, prior to any seizures (not shown), and matched control saline-treated animals. **(A)** 2DG autoradiography during discrete seizures. Focal uptake is seen in the (a) frontal pole, (b) orbital cortex, (c) midventral striatum, (d) ventromedial globus pallidus, (e) basolateral amygdala, and (f) substantia nigra pars reticulata. **(B)** 2DG during waxing and waning seizures. In general there is more activation of limbic structures at this stage. Activation is seen in the (a) anterior olfactory nucleus, (b) piriform cortex, (c) insular cortex, (d) nucleus of lateral olfactory tract, (e) amygdala and (f) entorhinal/perirhinal cortices. **(C)** 2DG during continuous seizures with fast and slow wave spiking. In addition to previously seen limbic activation, there is now widespread activation of cortical areas, thalamic nuclei, and basal ganglia. **(D)** 2DG during late continuous fast spiking. There is continued widespread increased glucose uptake, but with relative sparing of the globus pallidus, amygdala, entorhinal/perirhinal cortices, and substantia nigra compared to prior stages. (Reproduced from ref. *30* with permission.)

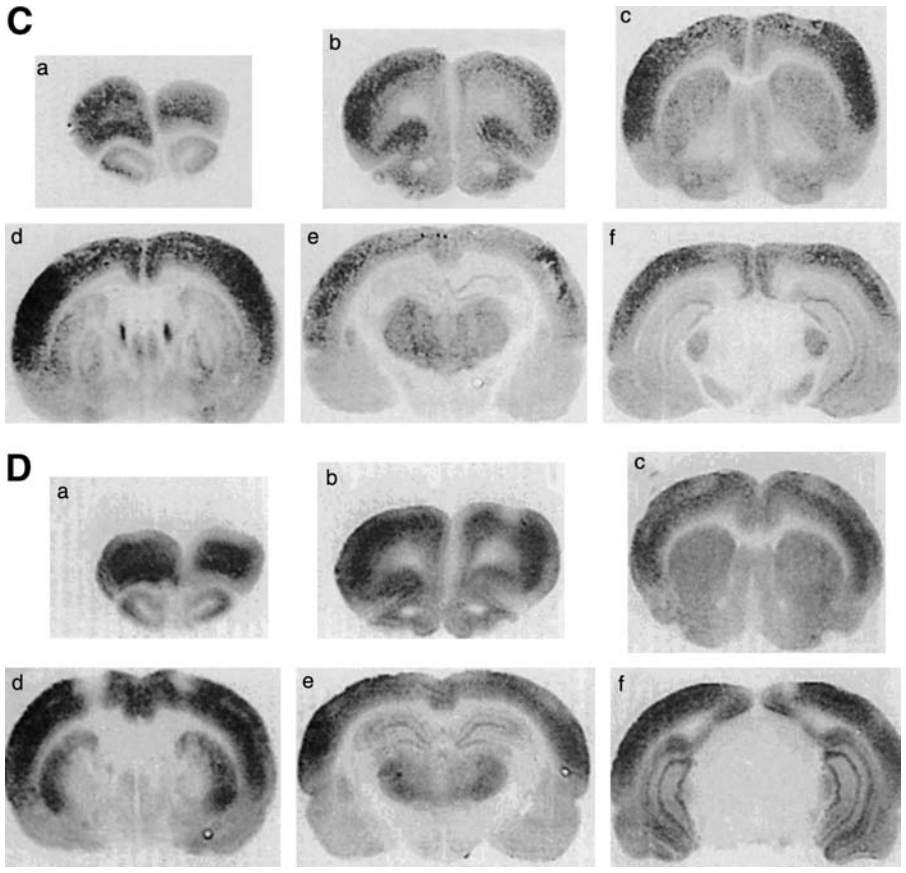

Fig. 4. *(Continued)*

system, the dentate gyrus serves as a "gatekeeper" and prevents excitatory stimulation from spreading through the hippocampus until a point of maximal dentate activation is reached *(27)*. Once this point is exceeded, excitatory inputs can spread through the hippocampus and may then propagate to involve widespread neocortical areas. In the autoradiography studies by Handforth and Treiman, as SE evolved from discrete seizures to waxing and waning seizure activity, and finally to late continuous fast spiking on EEG, there was an orderly progression of anatomical involvement, initially involving rostral cortical and olfactory regions, followed by involvement of additional limbic and cortical structures and subcortical regions, and finally with widespread recruitment of most forebrain areas *(30)* (Fig. 4). As status epilepticus continued, eventually reaching the stage of periodic epileptiform discharges, ongoing changes occurred in anatomic regions involved, ultimately reaching a stage where increased activation was lost, or

even depressed, with most forebrain regions showing decreased glucose utilization, with the exception of residual hyperactivation in the hippocampus *(31)*.

4.2. GABA Mechanisms

Gamma amino butyric acid (GABA) is the main inhibitory neurotransmitter of the central nervous system. It is made from glutamate by glutamic acid decarboxylase (GAD). There are two main classes of neurotransmitter receptor systems: *ionotropic* describes a receptor where the neurotransmitter's effects are mediated by the movement of an ion through an ion pore or channel, and *metabotropic* describes a receptor where the neurotransmitter's effects are mediated by a second messenger system. GABA binds to at least two receptor systems after its release from the presynaptic membrane. $GABA_B$ receptors are metabotropic (leading indirectly to increased K conductance), and $GABA_A$ receptors are ionotropic (leading directly to increased Cl conductance), both being responsible for IPSPs *(32)*. A number of GABA antagonists can precipitate status epilepticus, pointing to the primary importance of GABA in seizure generation. Other data support the concept of failure of inhibitory mechanisms as SE progresses, thought to be due to a "failure of GABA" mechanism. In both in vivo and in vitro models, GABA-mediated drugs that are efficacious early in SE seem to fail or be less effective as SE progresses *(33,34)*. For example, the $GABA_A$ agonist diazepam is less effective in ameliorating SE when administered after perforant path stimulation than when administered earlier (Fig. 5). When diazepam was given before 60 min of perforant path stimation, seizures were virtually eliminated (Fig. 5A). When diazepam was given after 60 min of perforant path stimulation, however, SE was shortened in duration by only approximately one half (Fig. 5B, E). Interestingly, similar refractoriness to therapy was also seen in this model with phenytoin, which is thought to work primarily by blocking voltage-gated cation channels (Fig. 5A,B). Decreased effectiveness of antiepileptic medications as SE progresses is also supported by other experimental work *(35)* and by clinical experience.

One possible mechanism for this decreased effectiveness is a failure of inhibitory GABAergic neurotransmission. Following status epilepticus, hippocampal neurons are less responsive to GABAergic agonists and are more depolarized than are naïve neurons *(36,37)*. Under some conditions, downregulation of GABA function can also occur by endocytosis of components of $GABA_A$ receptors *(38)*. Thus, rapid changes in GABA receptor properties may play a role in sustaining SE. Other data show that high-frequency stimulation of rat hippocampal neurons can produce strong depolarizing currents mediated by $GABA_A$ receptors and suggest that the ability to produce this kind of excitatory responses is likely mediated by a bicarbonate-dependent increase in the extracellular K concentration *(39)*. In addition, as lessons from developmental biology have shown, GABA is excitatory in immature neurons before it becomes inhibitory. The mechanism of the switch is multifactorial but includes a change in receptor types and a decrease in intracellular chloride

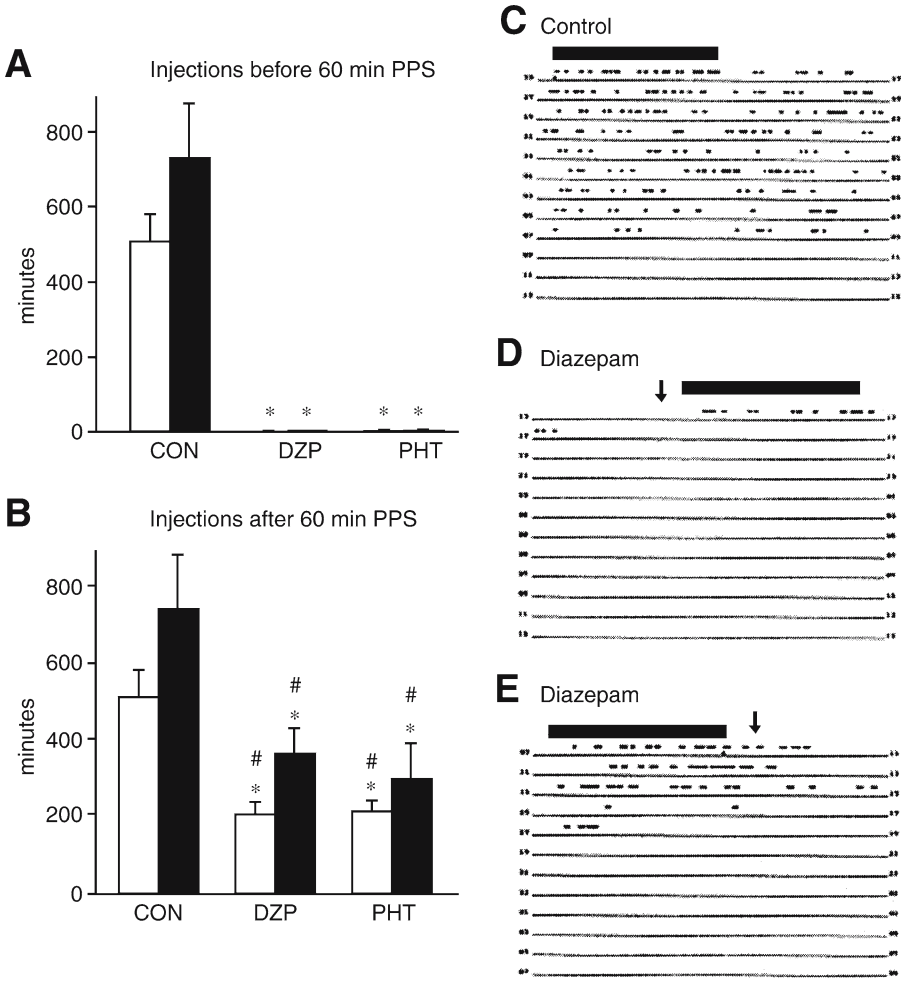

Fig. 5. The ability to reverse status epilepticus after perforant path stimulation (PPS). Effects of diazepam (DZP) and phenytoin (PHT) on self-sustained status epilepticus (SSSE) induced in rats by 60 min of PPS *(43)*. **A** and **B** plot minutes of seizures under different drug conditions. Open (white) bars show time spent in seizures and closed (black) bars show the occurrence of the last seizure in SSSE. In **A**, when drugs were administered before perforant path stimulation, both drugs prevented the establishment of SSSE. In **B**, when drugs were given 10 min after PPS, neither drug aborted SSSE, but both shortened SSSE duration. $^{*}p < 0.05$ compared with control (CON). $^{\#}p < 0.05$, DZP and PHT in part **B** compared with A (posttreatment compared with pretreatment). **C**–**E** show representative time courses of seizures, with each line representing 2 h of electrographic monitoring and each black bar representing a software-recognized seizure. **C** is control animal, **D** is an animal that was injected with DZP 10 min before PPS, and **E** is an animal that was injected with DZP 10 min after PPS. Perforant path stimulation is denoted by the thick bar on top of each segment

(Cl^-) *(40)*. Thus, there may be states in the mature brain where GABA may revert to being excitatory, depending on the ionic milieu *(41)*, and it is possible that this may play a role in SE. For instance, one can conceptualize that the usual Cl^- influx that is mediated by the $GABA_A$ receptor, which causes a hyperpolarization (inhibition), could, with repetitive seizures and GABA release, lead to a buildup of intracellular Cl^- and a change in the concentration gradient of Cl^- so that after repetitive firing, Cl^- could go down its concentration gradient, efflux out of the cell, and contribute to a depolarization.

4.3. Glutamate Mechanisms

Glutamate is the main excitatory neurotransmitter in the central nervous system. Glutamate acts on several receptor systems, which can be summarized as ionotropic NMDA, ionotropic non-NMDA, and metabotropic receptors. Several glutamate receptor agonists can induce SE (Table 2). Non-NMDA ionotropic glutamate receptors are thought to be responsible for the early component of the excitatory postsynaptic potential (EPSP), opening channels that allow movement of mainly Na^+ and K^+. NMDA receptors contribute to the late component of the EPSP, and also allow passage of Ca^{2+}. For maximal activation of NMDA receptors to occur, the membrane must first become partially depolarized by the activation of non-NMDA receptors to allow Mg^{2+} (which usually sits in a pore on the NMDA receptor) to unblock the channel and allow influx of Ca^{2+} into the cell. This may then activate Ca^{2+}-mediated second messenger pathways (not unique to SE) leading to cell injury and destruction.

Studies of rat electrogenic SE suggest that NMDA receptors may be important for the maintenance of SE (Fig. 6) *(42,43)*. When the NMDA blocker MK-801 was given after perforant path stimulation, SE was almost immediately aborted, while under control conditions, SE continued for many hours (Fig. 6A,B). Non-NMDA receptor blockers such as CNQX (*see* Fig. 6C) abolished seizures for several hours, although the underlying brain excitability was unchanged, and when the drug wore off, SE continued in full force. Thus, NMDA receptor activation may be a crucial excitatory process underlying SE, although it is likely that NMDA receptor activation occurs as a final common pathway triggered by many possible routes to SE.

4.4. Neuropeptides

In addition to GABA and glutamate, many other substances and receptor systems are likely to be involved in status epilepticus. A variety of agents (e.g., lithium/pilocarpine, domoic acid, bicuculline), which act on different receptor systems, can be used to

Fig. 5. *(continued)* and injection of DZP denoted by thick arrows. Note that in pretreated animals **(D)** only a few seizures were observed after PPS, and in posttreated animals **(E)** seizures continued for 8 h compared with 17 h in the control. (Reproduced from refs. *34* and *43* with permission.)

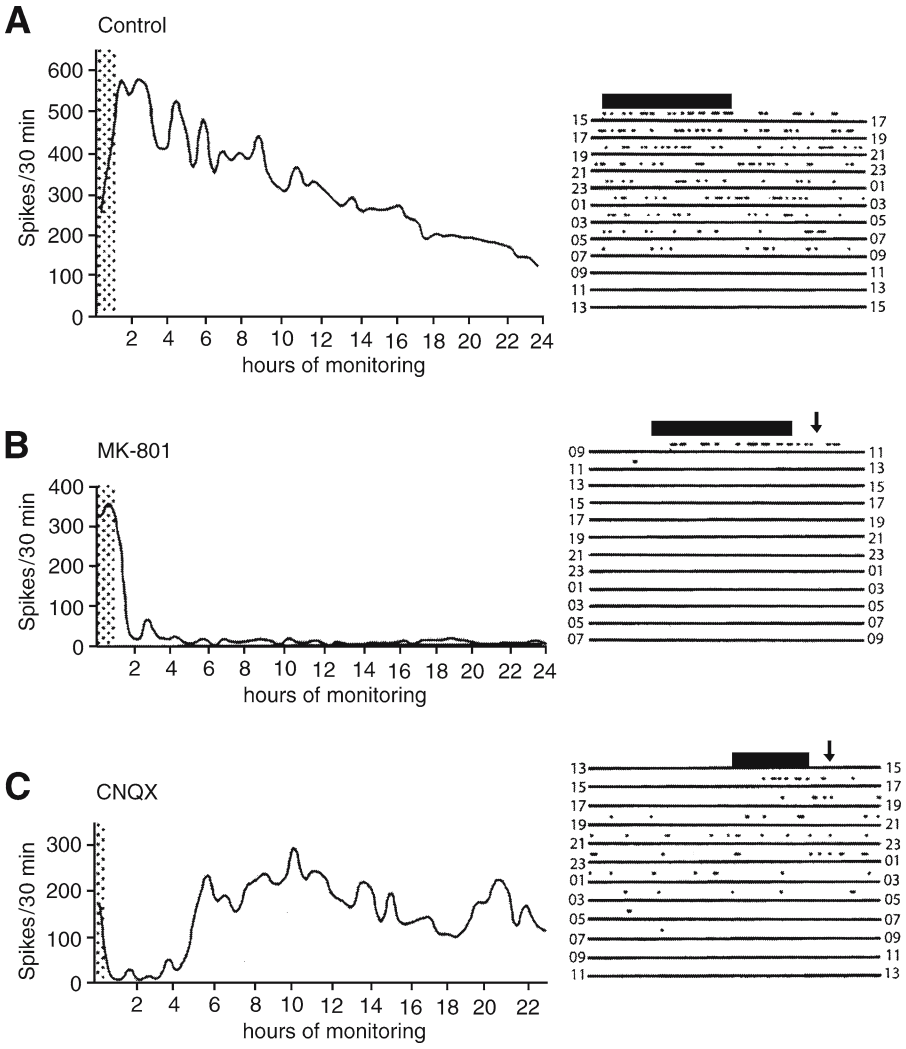

Fig. 6. The effects of NMDA and non-NMDA receptor blockers on self-sustaining SE induced by PPS in the rat. Each graph shows frequency of spikes per 30-min period plotted against the time course of self-sustaining SE. Perforant path stimulation is indicated by the gray bar. Next to each graph is a representative example that shows the time course of seizures detected by the software, with each line representing 2 h of monitoring and each seizure by a black bar. Note that under control conditions, PPS induced prolonged epileptiform activity **(A)**. The NMDA blocker MK-801 administered 10 min after perforant pathway stimulation **(B)** irreversibly aborted status epilepticus, but CNQX (a non-NMDA receptor blocker) injection **(C)** only induced transient suppression of seizures, which reappeared 2–4 h after injection. (Adapted from refs. *42* and *43* with permission.)

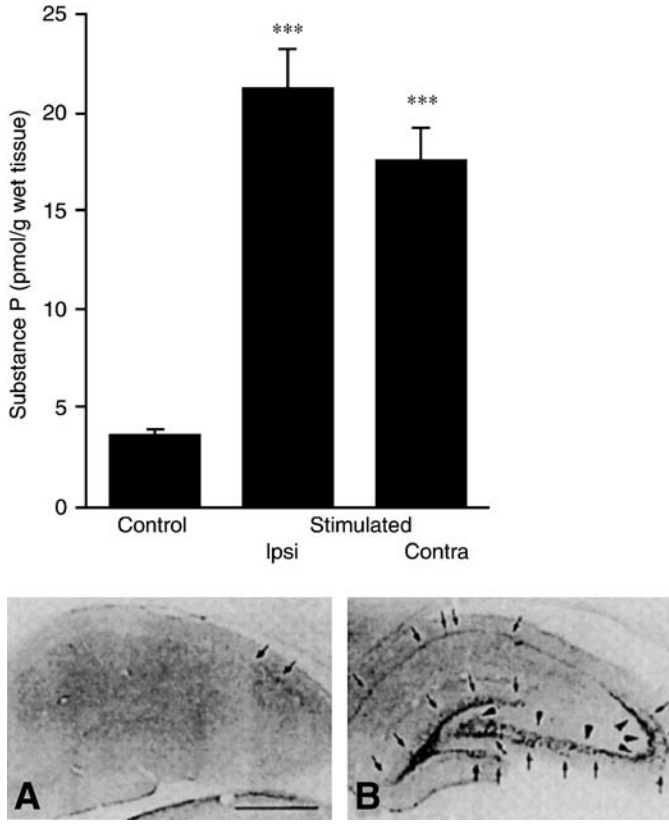

Fig. 7. (top) Subtance P content as measured by ELISA of the hippocampus 24 h after the end of 30 min of perforant path stimulation. (Reproduced from ref. *44* with permission from the publisher, PNAS.) Bottom, (**A)** Under control conditions, few SP-immunoreactive fibers are seen at the junction of CA2 and CA3 (arrows) and a few substance P-immunoreactive cells are present in stratum oriens of CA1 and CA2. (**B)** 24 h after SE induced by PPS, there is a dramatic increase in substance P-immunoreactive cell bodies in CA3, CA1, and granule cell layer (arrows) and mossy fibers (arrowheads). (Reproduced from ref. *43* with permission.)

initiate SE experimentally, and a number of substances can be used to ameliorate SE, especially in the early stages (*see* Table 2). Neuropeptides may play an especially important role in modulating the initiation and maintenance of SE.

Some data seem to support a key role for substance P (SP) as a proconvulsant in status epilepticus *(43,44)*. Substance P and neurokinin B are neuropeptides of the tachykinin family. Substance P is widely distributed in the central nervous and is involved in a number of physiologic processes, such as nociception and inflammatory responses *(44)*. As shown in Fig. 7, substance P increases in the rat hippocampus after SE is induced by perforant path stimulation. Immunostaining for SP receptors after

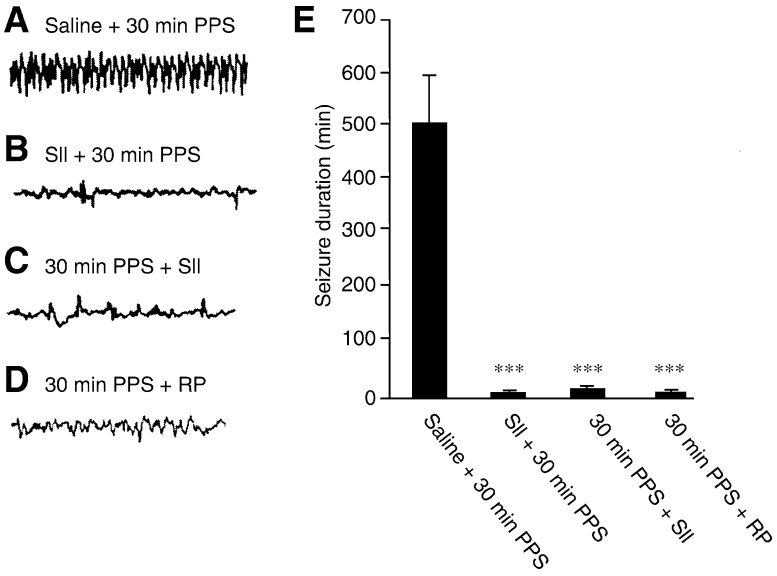

Fig. 8. Effects of substance P receptor antagonists, spantide II (SII) and RP-67,580 (RP), on duration of seizures. (**A–D)** are representative EEGs from hippocampal dentate gyrus 30 min after the end of 30 min PPS. (**E)** summary of effects of substance P receptor antagonists on the duration of seizures induced by 30 min of perforant path stimulation (PPS). Thirty minutes of PPS induced seizures lasting an average of 506 ± 100 min, but when pretreated with 1 nmol SII, mean seizure time decreased to 5 min. More importantly, injection of 50 nmol SII, or 25 nmol RP-67,580 10 min *after* PPS reduced mean seizure duration to 8 min and 6 min, respectively. (Reproduced from ref. *44* with permission.)

SE shows a dramatic increase in the number of SP immunoreactive cell bodies in CA3, CA2, granule cells, and mossy fibers. A variety of other data point to an important proconvulsant role of SP. For example, seizure duration is markedly decreased when SP antagonists are given to animals after 30 min of perforant path stimulation (Fig. 8) *(44)*. SP's action appears to be mediated by SP receptors. The production of substance P seems to be upregulated in SE, and may play a maladaptive role in the maintenance of SE, prolonging seizure duration. In further support of this, homozygous knockout mice for preprotachykinin (PPT)-A, a precursor of substance P and neurokinin A, are resistant to SE induced by kainic acid or pentylenetetrazole *(45)*. Additional studies have shown that SP enhances glutamate release from hippocampal slices, suggesting that enhanced glutamatergic neurotransmission may contribute to the proconvulsant effects of SP (Fig. 9) *(44)*.

While substance P seems to have an important role as a proconvulsant, other neuropeptides have anticonvulsant effects that may play a role in status epilepticus *(46)*. Galanin, another widely distributed neuropeptide, has anticonvulsant properties. In contrast to SP, galanin receptor density in the hippocampus is high at baseline. Multiple subtypes of galanin receptors have been cloned *(47,48)*. Galanin has been

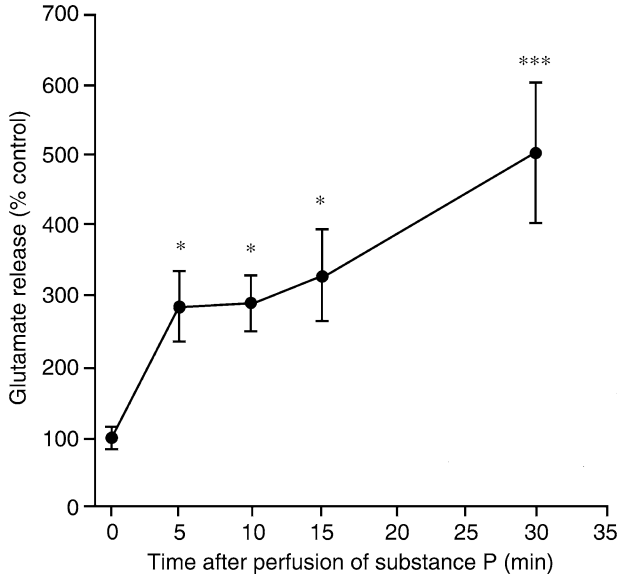

Fig. 9. Time course of perfusate concentration of glutamate in response to superfusion of hippocampal slices with 1μ*M* substance P. Basal concentrations are determined as mean values from six consecutive fractions before treatment with substance P (0 min), and subsequent assays are expressed as the percent of basal concentration. (Reproduced from ref. *44* with permission.)

shown to have potent effects on SE in rats (Fig. 10) *(49)*. When galanin is injected locally after 30 min of perforant path stimulation (PPS), SE is aborted (Fig. 10B). In addition, although 7 min of PPS is not usually enough to precipitate SE, when animals are pretreated with galanin receptor antagonists, 7 min of PPS is enough to produce prolonged SE (Fig. 10C,D) *(50)*.

Interestingly, while galanin is a potent blocker of SE, hippocampal galanin is rapidly depleted during SE, and galanin immunoreactive neurons disappear following status epilepticus induced by perforant path stimulation or by lithium/pilocarpine *(50)*. In addition, galanin release may be decreased during SE through inhibition of galanin containing neurons in the medial septum that project to the hippocampus *(49)*.

Other substances that can modulate status epilepticus include opioids (Table 2). Studies from the rat show that κ opioids are anticonvulsant, while δ opioids are proconvulsant and seem to facilitate seizure initiation but do not affect the maintenance of SE *(46,51)*.

5. MAINTENANCE AND TERMINATION OF STATUS EPILEPTICUS

As discussed earlier, the initial stages of status epilepticus are likely modulated by many mechanisms, and can be interrupted relatively easily. Later in SE, however,

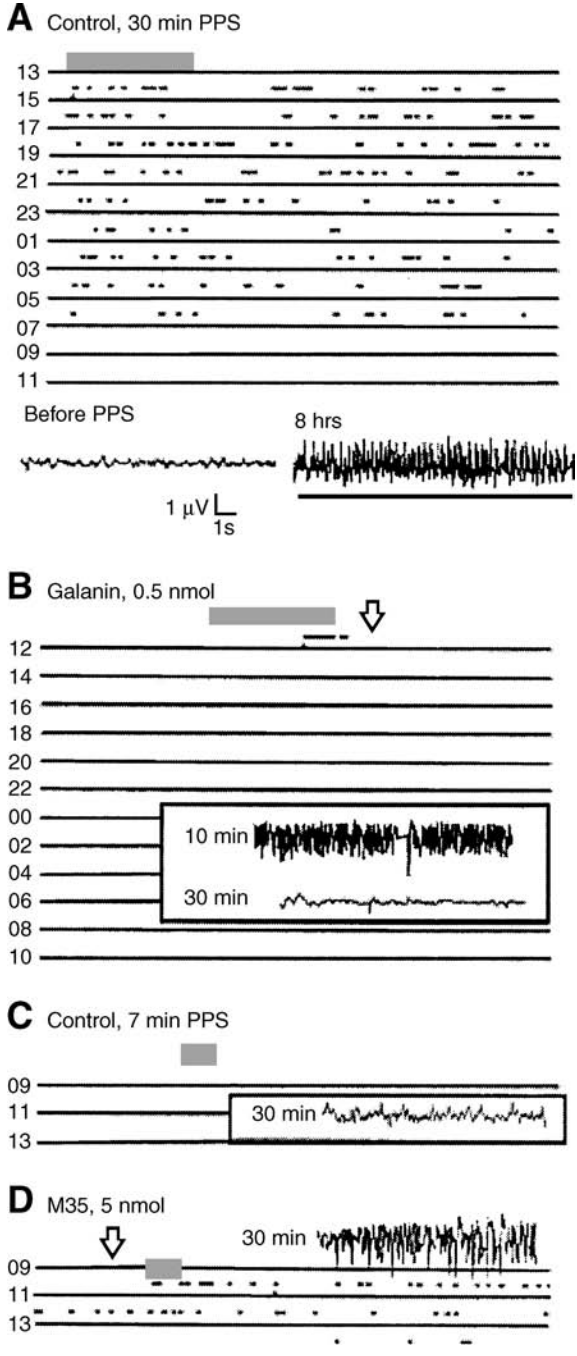
A Control, 30 min PPS
13
15
17
19
21
23
01
03
05
07
09
11
Before PPS
8 hrs
1 μV
1s
B Galanin, 0.5 nmol
12
14
16
18
20
22
00
02
04
06
08
10
10 min
30 min
C Control, 7 min PPS
09
11
13
30 min
D M35, 5 nmol
30 min
09
11
13

Fig. 10.

fewer agents are known to abort SE as the process continues (Table 2) and seizures become more refractory to anticonvulsant medications (Fig. 5) *(34,43)*. A physiologic transition occurs after 30 to 60 min of SE (Fig. 1), and different brain regions are involved later in the course of this disorder (Fig. 4).

In animal models (Table 2), the most effective agents in aborting the maintenance stage of SE are NMDA blockers, substance P antagonists, galanin, and dynorphin. Maladaptive changes, such as increased SP and decreased galanin, may contribute to the maintenance of SE *(49)*. In addition, whereas GABA is the main inhibitory neurotransmitter, many potential mechanisms contribute to the failure of this inhibition during status epilepticus, including GABA receptor endocytosis, decreased presynaptic GABA release, GABA receptor subunit rearrangement, and GABA-mediated depolarization *(49)*. Modulation of excitatory mechanisms, particularly NMDA receptor-mediated glutamatergic transmission, is likely another crucial mechanism involved in maintenance and cell damage associated with SE. Substance P may promote seizures through enhanced glutamatergic neurotransmission, while mechanisms of other neuropeptides in modulating SE are still under investigation.

Surprisingly little is known about endogenous mechanisms for termination of sustained status epilepticus. While inhibitory mechanisms may play an important role in terminating individual seizures, it is the failure of precisely these mechanisms that appears to contribute to the initiation of SE, making it difficult to explain how they might participate in termination of SE. Possible mechanisms contributing to terminating SE may include neuronal injury, depletion of metabolic stores, depletion of excitatory neurotransmission, or late enhancement of inhibitory mechanisms. Some investigators have followed the cerebral metabolic rate for glucose *(30,52)*, which increases tremendously in early SE and then normalizes and falls as SE progresses and have correlated the fall in the cerebral metabolic rate with the occurrence of neuronal damage. This points to the role of metabolic depletion and neuronal injury in termination of SE in a very indirect way. Some possible evidence for late enhancement of inhibitory mechanisms come from work with galanin, which shows that although galanin (an endogenous anticonvulsant) is depleted early in the course of SE, staining for galanin interneurons reappears in the dentate hilus in the late stages of SE *(34)*.

Fig. 10. Effects of galanin on status epilepticus *(50)*. **(A)** (top): representative time course of self-sustaining status epilepticus under control conditions. Each line represents 2 h of monitoring. The duration of perforant path stimulation (PPS) is indicated by the large gray bar. Each electrographic event recognized as a seizure is indicated by a small horizontal black bar. **(A)** (bottom): representative recordings before and 8 h after PPS. **(B)** representative tracing from rat injected with intrahippocampal galanin 10 min after the end of PPS (arrow). **(C)** representative tracing after 7 min of PPS with sample EEG taken 30 min after PPS showing no epileptiform activity. **(D)** representative tracing that shows the effect of pretreatment with M35, a galanin receptor antagonist, on the ability of the animal to establish self-sustaining SE. In contrast to **C,** this animal developed self-sustaining SE lasting for 3 h with only 7 min of PPS. (Reproduced from ref. *50* with permission.)

6. CONCLUSIONS

Status epilepticus is a complicated phenomenon that is likely the end result of many possible precipitants. Based on work with animal models, there appear to be many factors that can promote the initiation of SE and cause a shift in excitatory over inhibitory factors. GABA, the usual potent inhibitory neurotransmitter, fails possibly because it becomes excitatory with overstimulation, or possibly from other local changes. Glutamate appears to mediate the final path to sustained seizures and ultimately to destruction of neurons. Neuropeptides such as dynorphin, substance P, and galanin are potent modulators of the process and may affect the maintenance phase of SE. Local circuits, such as structures in the limbic system, are recruited early in SE, while later, intense activity occurs in more widespread networks.

These studies suggest that for the clinician, the main message is to treat early and aggressively with therapeutic doses of medications, before the cellular, molecular, and physiologic changes heralding maintenance of SE can be initiated. It is hoped that promising new agents will be developed that will improve outcome even when administered after maintenance of status epilepticus has been established.

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9

Cellular Damage and the Neuropathology of Status Epilepticus

Nathan B. Fountain

1. INTRODUCTION

The neuropathology of status epilepticus (SE) is well established. This chapter will review the histopathology and pathophysiology of cellular damage associated with SE based on observations from human cases and experimentally induced SE. The mechanisms of hyperexcitability leading to excitotoxic cell death will be discussed. This chapter concentrates on human generalized convulsive status epilepticus (GCSE) because it is most relevant, but the complementary nature of experimental findings from animal research will be emphasized.

Neuronal injury due to GCSE causes acute and chronic neurologic sequelae, while mortality typically results from systemic effects of GCSE. Neuronal injury causes chronic neurologic complications of epilepsy and encephalopathy that are discussed here. Systemic physiologic changes causing mortality will not be discussed here because they are only indirectly related to neuronal injury and are covered elsewhere, particularly in Chapter 6.

2. CLINICAL EVIDENCE OF NEURONAL INJURY

Neuronal damage due to GCSE is manifest as the subsequent development of neurologic symptoms, such as encephalopathy and epilepsy. About 40% of patients develop epilepsy after SE, and some patients develop focal neurologic deficits. There are also surrogate or indirect markers of neuronal injury, including radiologic and biochemical findings.

2.1. Neurologic Deficits as Evidence of Neuronal Injury

The incidence of specific neurologic findings after GCSE is surprisingly low. Dodrill and Wilensky found few reports of documented decline in mental ability after status epilepticus, although there are several uncontrolled case series that report a decline incidental to other findings *(1)*. In their own prospective study of nine epilepsy patients with SE and matched epilepsy patient controls, they found a trend

From: *Current Clinical Neurology: Status Epilepticus: A Clinical Perspective*
Edited by: F. W. Drislane © Humana Press Inc., Totowa, NJ

toward decline in three of four tests of mental ability administered. Focal neurologic findings after GCSE have rarely been reported, which is not surprising because the pattern of cellular injury from GCSE is unlikely to affect the motor system, as discussed below. Aicardi and Chevrie reported that 9 to 11% of children had focal signs after GCSE, but those findings were almost entirely attributable to the primary etiology of GCSE, rather than to the GCSE itself *(2)*.

2.2. Epileptogenicity of Status Epilepticus

GCSE may cause epilepsy or be the presenting seizure in patients with epilepsy of another cause. The epileptogenic potential of GCSE has been reviewed *(3,4)*. The incidence of epilepsy after GCSE is a relatively simple epidemiologic problem to solve. Hesdorffer and colleagues reported that out of 199 cases of status epilepticus more than 15% developed epilepsy, and others have found GCSE to be the presenting seizure in about 20% of patients with epilepsy *(5–7)*. Determining what proportion of epilepsy results directly from the SE rather than the underlying etiology is more problematic. In a separate study, Hesdorffer and colleagues found a 3.3-fold increased risk for epilepsy after status epilepticus compared to the occurrence following a single acute symptomatic seizure *(8)*. At 10 yr of follow-up, 41% of those with SE due to an acute symptomatic cause had epilepsy, compared with 13% of patients after a single acute symptomatic seizure. By using acute symptomatic seizures as the comparison group, this retrospective epidemiologic study controlled for etiology and severity as best possible. Data reviewed below demonstrate that at least some patients develop temporal lobe epilepsy due to mesial temporal sclerosis after SE. Thus, there is compelling clinical evidence that GCSE causes temporal lobe epilepsy in some cases, providing indirect evidence that GCSE causes neuronal injury.

2.3. Radiologic Evidence of Neuronal Injury

Radiologic changes during or after GCSE provide a surrogate for neuropathologic changes, which otherwise require examining tissue. The acute changes during or following GCSE have been reported in individual cases and small case series. MRI changes of acute edema have long been recognized after GCSE and partial status epilepticus *(9)*, and progressive hippocampal atrophy has been demonstrated. Nohria and colleagues performed serial MRIs during and after repeated episodes of GCSE in a previously normal 32-mo-old child who developed subsequent complex partial seizures *(10)*. They found an acute increase in T2 signal and enlargement of the hippocampus, suggesting edema, and the later development of unilateral hippocampal volume loss and increased T2 signal, suggesting hippocampal sclerosis. Tien and Felsberg reported on a series of five patients, two with GCSE and three with nonconvulsive status epilepticus (NCSE), all of whom had acute changes of hippocampal edema *(11)*. Subsequent bilateral hippocampal atrophy developed in the GCSE patients, and unilateral hippocampal atrophy developed in two NCSE patients who were available for follow-up.

Other case reports and case series have generally substantiated these findings *(12,13)*.

MRI evidence of acute hippocampal edema is a consistent finding, but progressive hippocampal atrophy is not a universal feature. Salmenpera and colleagues performed a prospective volumetric MRI study of nine patients with GCSE and one with NCSE, compared to age- and sex-matched controls, at 3 wk, 6 mo, and 1 yr after status epilepticus *(14)*. This careful study did not find evidence of atrophy. The average duration of SE was only 1 h and 44 min, and only one patient had SE for longer than 2 h. Therefore, it is possible that the duration or severity of SE was not sufficient to result in detectable damage. Henry and colleagues reported two cases of typical acute MRI changes immediately after NCSE *(15)*. One patient had a normal MRI 9 wk later, and the other had an astrocytoma.

2.4. Biochemical Evidence of Neuronal Injury

There is biochemical evidence of neuronal injury during status epilepticus. Neuron-specific enolase is an intracellular enzyme that is released during neuronal injury. DeGiorgio and colleagues have reported consistently increased levels of neuron-specific enolase in CSF and blood from patients immediately after SE *(16–19)*. In an attempt to parse out which types of SE have the greatest degree of injury, this group has reported the greatest elevations with complex partial SE and "subclinical" SE. The elevations were significant in all types of SE, however, so it is difficult to know the biological significance of a greater elevation in one group. Elevation of neuron-specific enolase undoubtedly implies neuronal injury, but it is less clear whether it is a marker of neuronal death. This group reported elevations after single seizures, but there is little evidence that a measurable number of neurons die with each seizure. Therefore, it may be a marker of neuronal injury only.

3. CHARACTERISTICS AND DISTRIBUTION OF NEUROPATHOLOGY

3.1. Hippocampal Histopathology

There is clear region-specific cell loss resulting from GCSE. Historically, the neuropathology of status epilepticus was of little interest until the 1950s, when the association of GCSE and temporal-lobe epilepsy was made. Meyer and colleagues described a single case of the neuropathologic changes after GCSE in 1955 *(20)*, and in 1964 Norman reported the findings in 11 children *(21)*. The seminal report of Corsellis and Bruton describing the location of cell loss in autopsy cases of patients dying in GCSE *(22)* is still relevant today and unlikely to be supplanted (even though their report lacks quantification) because large autopsy series are now uncommon.

Corsellis and Bruton reported autopsy findings from 20 patients who died during status epilepticus, taken from a total of 290 brains of epilepsy patients *(22)*. The sample included 8 children (6 without epilepsy) and 12 adults (all with epilepsy).

The most consistent and severely affected region was the hippocampus, which had gross edema and cell loss. Subsequent refinements have found cell loss and acute reactive gliosis in hippocampal areas CA1, CA3, and dentate gyrus. Cerebellar Purkinje cell loss and acute reactive gliosis are common but not always present or severe. This histologic change may be the basis for the common finding of cerebellar atrophy in epilepsy patients. Thalamic damage is even less consistent; there may be damage only within specific nuclei or foci. Occasionally, the striatum may be affected. The cerebral cortex suffers cell loss inconsistently and sometimes in a patchy distribution, especially in the middle layers. When other areas have been examined, cell loss has been reported in the claustrum *(23)*. There is little evidence that SE causes injury in other areas.

Corsellis and Bruton did not find brain pathology attributable to status epilepticus in two of the infants and eight of the adults. One could infer that adult neurons are less susceptible to SE-induced injury. In experimental models, however, young rat pups have more severe SE than adults, while suffering less histopathologic damage than seen in the mature brain *(24–26)*. It is also notable that the two children without acute neuronal injury had prior epilepsy, as did all the adults. A more parsimonious explanation, however, is that the epilepsy patients died of systemic effects of SE before histologically identifiable damage was induced. Whatever the explanation, this finding illustrates that not all SE leads to acute neuronal injury.

Autopsy findings in human GCSE are confounded by comorbid hypoxia, hypotension, infection, systemic illness, and postmortem changes. Fujikawa and colleagues reported three patients who died in focal motor SE in the hospital without other significant contributing factors *(27)*. They found neuronal loss and gliosis in the hippocampus, amygdala, dorsomedial thalamus, Purkinje cells of the cerebellum, and piriform and entorhinal cortices. Because these patients had only focal motor SE they were unlikely to suffer significant systemic physiologic changes, but it is difficult to exclude acute terminal hypoxia or other problems. DeGiorgio and colleagues performed quantitative comparison of regional cell loss in five patients dying of GCSE compared with "normal" controls and epilepsy controls matched for age, hypoxia, epilepsy, and alcohol abuse *(28)*. Neuronal densities were disproportionately decreased in CA1, CA3, and prosubiculum in patients dying of GCSE. This is the most definitive evidence that human GCSE causes region-specific cell injury by epileptic mechanisms, separate from systemic or cerebral metabolic insults.

3.2. Extrahippocampal Injury

There have been a few reports of more widespread cortical damage after status epilepticus, but each case has been complicated by hypoxia or other systemic problems. Knopman and colleagues reported cortical necrosis without hippocampal involvement in a woman with epilepsia partialis continua, but this patient also had multiple medical problems, including chronic obstructive pulmonary disease (COPD) and pneumonia, that contributed to hypoxic damage *(29)*. Soffer and colleagues reported a similar case of focal status with cortical damage in a patient with hypoxia, hyperthermia, and acidosis *(30)*. These cases had asymmetric damage, with

the more affected hemisphere being the site of seizure origin. This suggests that the ongoing seizure activity exacerbated the cellular injury that ultimately was caused by systemic conditions, and was not primarily due to status epilepticus.

4. NONCONVULSIVE STATUS EPILEPTICUS

Nonconvulsive status epilepticus (NCSE) has recently received much attention as a clinical entity, but its pathophysiology has been neglected. This is not surprising, as its very definition remains controversial *(31)*. It may be reasonable to generalize the pathophysiology from GCSE to NCSE, but there are compelling human and animal data to suggest that the neuronal pathophysiology is different *(32)*. In particular, GCSE is based on recurrent excess excitation activating excitotoxicity, as noted below. Absence seizures, on the other hand, are mediated by enhanced recurrent inhibition and thus do not activate excess excitation. It is possible that some patients with NCSE are similar to those with GCSE, with activated excitotoxicity leading to cellular injury. On the other hand, some patients with NCSE may have seizures similar to absence seizures and would not be expected to incur neuronal injury.

Clinical observations suggest that both the above hypotheses are correct, in that some patients seem to suffer neuronal injury and others do not. Although there is compelling radiologic evidence of focal hippocampal neuronal injury in human GCSE, the data regarding NCSE are less clear. There are many case reports, noted above, of acute hippocampal edema due to NCSE, but there are few focused reports about the long-term outcome from human NCSE and no data with regard to neuropathology. We found that 23 to 46% of patients developed epilepsy after NCSE as evidence of neuronal injury, but this is confounded by the presence of other brain disease and the possibility that NCSE is the presenting seizure in a patient with undetected epilepsy *(33)*. On the other hand, some have reported a lack of long-term morbidity *(34)*. As noted above, the most compelling evidence of neuronal injury is the presence of elevated neuron-specific enolase in some patients with NCSE *(16,17)*, but it is not known if this degree of "injury" results in neuronal death.

Overall, the clinical significance of NCSE remains controversial, in part because the classification and categorization of NCSE is complicated. We recently reported an overall mortality of 18% in 100 patients with NCSE *(35)*. Mortality was dependent on the etiology, rather than on traditional classification into absence and complex partial status epilepticus or EEG findings. Thus, it remains unclear whether, or under what circumstances, NCSE leads to neuronal injury.

5. ANIMAL MODELS OF STATUS EPILEPTICUS

5.1. Applicability of Animal Models

The clinical relevance of human findings is indisputable, but insight into specific aspects of the neuropathology is provided by the added degrees of control in experimental animal models of GCSE. Chemoconvulsant and electrogenic animal models of status epilepticus demonstrate that neuronal injury in the hippocampus and cortex is due to excessive neuronal activity of SE, while injury to the cerebellum and other

Table 1
Chemoconvulsant Models of Status Epilepticus

Systemic or Intracerebroventricular	Intracerebral
MDA	Kainic acid in amygdala
Quisqualate	Dibutyl cAMP into amygdala
Kainic acid	Folic acid into cortex
Domoic acid	Penicillin into cortex
Pentylenetetrazol	Bicuculline into cortex
Bicuculline	Picrotoxin into cortex
Allylglycine	Cobalt lesion + homocysteine
Pilocarpine ± lithium	
Soman	
Flurothyl	

areas is due primarily to fever, hypoxia, and other alterations of systemic physiologic parameters. This helps to explain why radiologic changes are limited to the hippocampus under the usual circumstances of adequate treatment of systemic physiologic parameters.

In reviewing animal experimental data, careful consideration must be given to whether the animal model used for a given experiment is applicable to the human condition. Acute generalized convulsive seizures can be induced in normal animals to simulate a seizure and, if allowed to continue, will become GCSE. GCSE may be induced by systemic or direct CNS exposure to convulsant substances. The most commonly used chemoconvulsants are pilocarpine and kainic acid, but many substances have been used (Table 1) *(32)*. Electrical stimulation can also induce SE, but usually of the nonconvulsive variety *(36)*. Therefore, caution should be exercised in interpreting whether any particular finding results from individual seizures or SE, whether SE was induced by a chemical or electrical method, and whether the situation genuinely recapitulates human GCSE.

5.2. Models of Status Epilepticus

Pilocarpine-induced GCSE is the most commonly used experimental model *(37)*. Systemic administration of pilocarpine, with lithium pretreatment, induces GCSE in rats, and this GCSE clinically and electrographically replicates human GCSE *(38)*.

The histopathologic findings of chemoconvulsant-induced experimental GCSE are similar, regardless of the chemoconvulsant administered. Meldrum and colleagues made pioneering contributions by examining GCSE induced by systemic bicuculline injection in baboons *(39–41)*. More common models used to induce GCSE in rats include systemic injection of pentylenetetrazol (PTZ), pilocarpine with or without lithium, flurothyl *(42)*, allylglycine *(43)*, and homocysteine after a focal cobalt lesion *(44)* (Table 1). GCSE can similarly be induced in piglets, mice, rabbits, sheep, and guinea pigs *(37,45–48)*. Intracortical injections of chemoconvulsants that produce GCSE include folate, penicillin, bicuculline, and picrotoxin *(49)*.

Status epilepticus more or less isolated to the limbic system can be induced by specific experimental protocols. Limbic SE can be limited to a nonconvulsive status epilepticus, avoiding the systemic physiologic effects of GCSE. Systemic kainic acid *(47,50,51)*, *N*-methyl-D-aspartate (NMDA), quisqualate, and domoic acid can be administered in a manner that preferentially activates the limbic system *(47,50–53)*. These are useful methods in and of themselves, but more importantly they implicate specific receptor systems in status epilepticus. The disadvantage of these methods in the search for SE-induced neuronal injury is that they may themselves be neurotoxic, such as with NMDA receptor-activating drugs (*see* Section 6.2.). It is impossible to state clearly whether the sequelae of SE so induced are solely the result of SE or are due to the chemoconvulsant itself, independent of its ability to induce status. Of practical importance is that they can induce systemic alterations, which could contribute to neuronal injury.

Electrogenic methods of inducing SE have the advantage of avoiding any possible direct toxic effect of chemoconvulsants *(54)*. A common model is to implant electrodes in the rat hippocampus (although most limbic sites will work) and then provide a period of continuous stimulation *(36,55)*.

5.3. Histopathology of Experimental Status Epilepticus

Histopathologic investigations from electrogenic and common chemoconvulsant models demonstrate patterns of cell loss identical to those in human GCSE. Bertram and colleagues found a quantitative loss of pyramidal neurons in CA1 of rats after electrogenically induced SE or rapid kindling *(56)*. Middle layers of the entorhinal cortex also suffer neuronal cell loss in this model *(57)*. Similar histopathology is found in the pilocarpine and kainic acid models *(37,58)*.

Overall, animal models of GCSE have solidified the findings from human autopsy studies that status epilepticus causes neuronal injury in the hippocampus and little injury elsewhere. Animal models of limbic SE cause injury that is identical to that in GCSE, which further suggests that it is the neuronal activity of SE that causes injury to the hippocampus rather than deriving from the systemic effects.

6. MECHANISMS OF CELLULAR DAMAGE

6.1. Neuronal Injury Is Not the Result of Systemic Factors

Animal experiments definitively demonstrate that hippocampal cellular damage results primarily from the abnormal neuronal activity of GCSE rather than from the systemic or cerebral physiologic changes associated with excessive motor activity. It is reasonable, however, to consider that neuronal injury could also result from the systemic or cerebral physiologic changes induced by GCSE. Early during generalized tonic-clonic seizure activity, there is relative homeostasis mediated by an autonomic surge that, among other things, increases blood supply to meet the extreme cellular demands of seizures *(59)*. Very late in GCSE, however, homeostatic mechanisms break down, leading to such insults as cardiovascular arrhythmias, myocardial infarction, and myoglobinuria-induced acute tubular necrosis,

among other changes, substantially increasing mortality *(32,60,61)*. During this very late period, systemic physiologic changes could contribute to neuronal injury. Siesjo and colleagues found that metabolic and oxygen demands outstripped supply during GCSE and that this mismatch between substrate supply and demand could contribute to brain injury in vulnerable areas *(62)*. This did not occur, however, until several hours into GCSE, and others did not find a decrease in cerebral blood flow until after at least 4 h, but found pathologic injury after much shorter periods of SE *(63)*.

The vital importance of this argument, of course, is that it implies that the intervention of muscle paralysis and routine critical care management could prevent these systemic changes and therefore would be expected to prevent neuronal injury. Meldrum and colleagues examined this in a series of careful systematic experiments. Muscle paralysis was used to prevent the motor manifestations of bicuculline-induced experimental GCSE in baboons. Paralysis prevented fever and eliminated cerebellar injury, but injury continued in the hippocampus *(39,40)*. The next logical step was to lock all systemic physiologic parameters in the normal range. Preventing elevated body temperature again reduced or eliminated cerebellar injury. Hippocampal injury persisted, however, even when body temperature, blood pressure, oxygenation, and serum glucose were clamped in the normal range *(64)*. This substantiates that hippocampal injury is due to intrinsic neuronal activity. Thus, muscle paralysis is not acceptable as a primary treatment for GCSE because it will not prevent hippocampal neuronal injury.

An important clue to the mechanism of seizure-induced neuronal injury comes from an experiment of nature. Canadian researchers reported that an acute neurologic syndrome, including seizures and SE, was due to ingestion of mussels from Prince Edward Island that were contaminated by domoic acid *(65,66)*. Domoic acid is structurally similar to glutamate and probably activates glutamate-mediated excitation. Of the 14 patients reported, five had clinically manifest seizures and three of these appeared to have SE. Of four patients who died, three had seizures or myoclonus, and there appears to have been consistent cell loss in hippocampal areas CA1, CA3, and CA4, with preservation of CA2. This pattern of cell loss is identical to that found in GCSE. Other areas were variably involved. At least one patient developed temporal lobe epilepsy and had autopsy findings of bilateral mesial temporal sclerosis reported in detail *(67)*. This strongly implies that glutamate-mediated mechanisms have a prominent role in neuronal damage during human GCSE.

6.2. Glutamate-Mediated Excitotoxicity

The principal identifiable mechanism of cellular damage during GCSE is glutamate-mediated excitotoxicity, although there are undoubtedly multiple other complex contributing factors. Glutamate is the most common excitatory neurotransmitter in the brain and binds to at least three subtypes of receptors: non-NMDA, NMDA, and metabotropic. Detailed reviews of excitotoxicity are available but the unique role of the NMDA subtype of glutamate receptor deserves special attention *(68,69)*.

Most normal excitatory neurotransmission is mediated by non-NMDA receptors, including the commonly identified subtypes of AMPA, kainate, and quisqualate. Simplistically, glutamate released from presynaptic nerve terminals binds to non-NMDA receptors and results in the short-duration opening of a sodium channel within the receptor. The excitatory postsynaptic potential (EPSP) induced results in generation of an action potential that conducts the discharge to the axon terminal and then to the next neuron.

Glutamate also binds to NMDA receptors, but under most circumstances the channel within the NMDA receptor does not allow any ion flow because the pore is blocked by a magnesium ion. When the neuron is sufficiently depolarized, such as during SE, the magnesium ion is released from the pore and ions flow. This self-perpetuating "use-dependent" property of the NMDA receptor is uniquely suited to sustain SE. The excitotoxic results are due to the detrimental effects of the influx of calcium ions through the pore and the prolonged nature of the depolarization, which allows yet more calcium to accumulate.

Excessive NMDA-mediated depolarization during GCSE results in necrotic cell death and delayed cell death, or apoptosis *(68)*. Necrotic cell death is probably due to the osmotic pressure and acute disruption of cellular processes caused by accumulation of cations, changes in intracellular potential, and protein abnormalities, such as abnormal phosphorylation *(70)*. Apoptosis is initiated by activation of immediate early genes, such as C-*fos*, and other processes in experimental GCSE *(71)*. It is becoming clear that necrotic and apoptotic processes are not entirely separate and may coexist *(72)*.

The delayed nature of some cell death induced by GCSE may be related to the observation that seizures often begin after a latent period. Other processes undoubtedly contribute, but programmed cell death and the cascade of cellular changes mediated by apoptosis are well suited for this role.

There is no single simple reason why the hippocampus is so seriously damaged by GCSE while other areas are spared. However, the hippocampus has several unique properties that predispose it to seizure-mediated injury. The hippocampus is the center of dissemination and propagation of limbic seizures. It potentially participates in a self-reinforcing circuit that would preferentially repetitively depolarize hippocampal neurons, increasing their risk of injury. The most compelling insight is that NMDA receptors are distributed primarily in the hippocampus; they are also scattered throughout the cortex, another area in the mammalian nervous system mildly injured in GCSE *(73,74)*.

7. SUMMARY

The histopathologic damage induced by GCSE is straightforward based on human clinical, radiologic, and histologic and animal experimental data. Severe damage is limited to the specific fields of the hippocampus, and mild damage occurs in the cortex. Additional damage in the cerebellum, thalamus, and basal ganglia results from systemic physiologic alterations. Glutamate-mediated excitotoxic

mechanisms play an important role in necrotic and apoptotic neuronal damage. The histopathology and pathophysiology of NCSE are less well defined but clearly occur across a larger spectrum, and at least some cases are similar to GCSE. Because neuronal injury is ongoing as long as seizure activity continues, patients who do not awaken immediately after treatment of status epilepticus must undergo EEG to exclude nonconvulsive status epilepticus or they risk potential neuronal injury.

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IV Nonconvulsive Status Epilepticus

10

Clinical Presentations of Nonconvulsive Status Epilepticus

Peter W. Kaplan

1. INTRODUCTION

There are descriptions of convulsions since neo-Babylonian times *(1)* reflecting the perception that an afflicted person was possessed by external forces or spirits. What was frightening to the observer was seeing a person possessed by a "seizure," with "outside forces" prevailing over the person's own control over mind and body. Occasionally such "possessions" were believed to be benign, but usually they were deemed to be evil, occasionally leading to ostracism of the individual from society or even relegation to an asylum.

In the West, clinical observations of seizures are mentioned by the ancient Greeks, Galen, and many physicians in the Middle Ages, with Eastern references by Avicenna *(2)*. As noted in the chapter on the history of status epilepticus in this book, there has also been more recent identification and description of status epilepticus. The French physicians Esquirol, Bouchet, and Cazauvielh made observations on some of these bizarre attacks in epileptics with such episodes of "epileptic delirium" and *fureur épileptique* noted after recovery from a convulsion and unconsciousness *(2)*. A state of wandering confusion was named "somnambulism," often without clear distinction in cause between a psychological sleeplike or an ictal state *(3)*. Such "lost" patients in "a kind of dreamland" were described by Sir Samuel Wilks, who referred even to this nonconvulsive state as "status epilepticus" and who was the first physician to use bromides regularly for the treatment of epilepsy *(4)*. Epileptic "fugue" states (in which the patient appeared to be "lost") were described by Prichard, Bright, and Hughlings-Jackson *(3,5,6)*, with the nature of these states remaining speculative given the lack of EEG correlate. On numerous occasions during his famous Tuesday morning lectures, Charcot presented a Parisian delivery man who wandered about Paris and farther afield in just such a clouded state, with spells also responsive to bromide therapy *(7)*.

The first documented case of absence status epilepticus (ASE) with an EEG correlate appeared in 1945 *(8)*, followed in 1956 by the identification of complex partial status epilepticus (CPSE) *(9)*. Yet, it has only been with the more recent use of video-EEG correlation that the wealth of clinical and behavioral correlates to nonconvulsive

From: *Current Clinical Neurology: Status Epilepticus: A Clinical Perspective*
Edited by: F. W. Drislane © Humana Press Inc., Totowa, NJ

states have been uncovered and identified. Many observations of bizarre behavior made in patients with known epilepsy, however, remain suspect unless correlated with simultaneous evidence of EEG seizure activity. Such states may otherwise be ascribed to postictal or interictal confusion or psychosis.

It has been almost 50 yr since status epilepticus was defined as a state of continuous seizures, or of several seizures without return to baseline neurologic state. More recent studies have underlined that 90% of patients will have seizures that remit spontaneously within 3 min, but when seizures last beyond this, they tend to endure for 10, 20, 30, or more minutes. Consequently, there has been renewed interest in establishing an early diagnosis and prompt treatment of convulsive status epilepticus in an attempt to diminish morbidity and mortality. The morbidity of nonconvulsive status epilepticus (NCSE) is more in contention, but it appears to vary from a 3% mortality when NCSE occurs in epilepsy patients without severe concurrent illness to mortality of 27% in patients with severe brain or systemic injury, rising to 39% if patients are deeply in coma *(10)*.

Identifying nonconvulsive states early in their course has been problematic. An allied state, electrical status epilepticus in coma, has often been an incidental observation in comatose patients in whom an EEG was obtained *(11)*. Milder states of obtundation, confusion, or even minimal changes in behavior in NCSE also represent scenarios in which NCSE is missed or overlooked, the obtundation often attributed to other causes of altered consciousness *(12)*. This chapter deals with the behavioral correlates in the different types of NCSE but will not address comatose states with electrical status epilepticus.

The cornerstone of diagnosis of NCSE is the correlation of EEG seizure activity to an observed alteration in cognitive function. At its simplest, NCSE may be defined as a condition of ongoing or intermittent clinical epileptic activity without convulsions, associated with EEG evidence of seizures. Unfortunately, there are several states of altered consciousness associated with epileptiform activity on EEG that are not NCSE: toxic encephalopathies with triphasic morphologies on EEG; comatose or obtunded states with periodic lateralized epileptiform discharges (PLEDs); and metabolic encephalopathies with EEGs containing interspersed epileptiform morphologies. These patients often show "improvement" in their EEG following IV benzodiazepines with a decrease in EEG epileptiform morphologies, but without a corresponding improvement in mentation *(13)*. The physician, therefore, is confronted even at the time of diagnosis by the need for accurate EEG interpretation and electroclinical correlation (Table 1). The issue of correct EEG diagnosis of NCSE has been the subject of a number of papers and reviews. Although it has been suggested that response to benzodiazepines could offer a defining point for NCSE, several studies have shown that clinical resolution with improvement in consciousness may be delayed for hours if not days in NCSE, and hence such cases remain *probable* NCSE rather than *definite*.

Official classification of status epilepticus has not yet been adopted by the International League Against Epilepsy (ILAE), but classifications have been suggested on the basis of etiology, clinical phenomenology, pathophysiology, and EEG characteristics *(14,15)*. Further problems arise because many cases of focal onset NCSE may appear to be generalized at the time of EEG, and hence are classified with the generalized forms.

Table 1
Electroencephalographic Differential Diagnosis of NCSE

Artifactual
Rhythmic, regular or paroxysmal muscle movement, ECG, or ballistocardiographic artifacts
Physiologic rhythmic patterns or patterns of nonictal significance
Rhythmic midtemporal theta of drowsiness
Subclinical rhythmic epileptiform discharges of adults (SREDA)
Pathologic epileptiform patterns
PLEDs
PLEDs plus
BiPLEDs
GPEDs
Triphasic waves (e.g., in hepatic dysfunction, uremia, anoxia; hyperammonemia; toxicity/drugs)
Rhythmic delta activity
Other abnormal EEG patterns that normalize concurrently with clinical improvement after IV benzodiazepines (benzodiazepine-responsive withdrawal encephalopathy)

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2. CLASSIFICATION

Nonconvulsive status epilepticus (NCSE) has been divided into two groups, largely along electroencephalographic criteria: (1) absence status epilepticus (ASE), a form of generalized nonconvulsive status epilepticus (GNSE), and (2) a lateralization-related nonconvulsive state, referred to as complex partial status epilepticus (CPSE).

Each of these groups has been subdivided further. GNSE includes (1) patients with a history of childhood absences characterized by three-per-second spike-and-waves (ASE); (2) patients with childhood-onset, secondary generalized epilepsy, usually with mental retardation, more marked confusion and myoclonus; (3) elderly patients presenting *de novo*, usually in association with a toxic or metabolic dysfunction, psychotropic medications or benzodiazepine withdrawal, or triggered by a tonic-clonic seizure; and (4) generalized nonconvulsive status epilepticus from partial onset of temporal or frontal origin.

The behavioral correlates of different types of NCSE arise from—or are at least associated with—different areas of maximal involvement of seizure activity identifiable by EEG. Hence the proclivity of seizure activity for frontal, mesial temporal, neocortical temporal, and temporo-parieto-occipital junctional regions has come to be correlated with particular symptomatic or behavioral features particular to those brain regions. Additionally, such presentations are seen to occur with certain underlying associated conditions such as mental retardation, uremia, or Alzheimer's disease, and therefore achieve clinical expression within the framework of the age of the patient. There are, therefore, particular clinical features typically seen in infants, small children, adults, or the elderly, although there is considerable overlap. A classification of nonconvulsive ictal states based on localization-related EEG criteria as well as age of expression and particular epileptic syndromic context is provided in Table 2.

Table 2
Classification of Nonconvulsive Ictal States

I. Generalized nonconvulsive status epilepticus (GNSE)

A. Absence status epilepticus (ASE)

i. Typical absence status epilepticus (TAS) occurring in idiopathic generalized epilepsies, with 3/s spike-and-wave
ii. *De novo* reactive (situation-related) absence status in the elderly, usually with neuroleptic medications, or following drug withdrawal
iii. Absence status with degenerative generalized epilepsies; progressive myoclonic epilepsies
iv. Secondary generalized NCSE of frontal or temporal lobe origin

B. Atypical absence status epilepticus (AASE)

i. Seen in childhood with secondary generalized epilepsy, usually with mental retardation (cryptogenic and symptomatic) e.g., with Lennox-Gastaut syndrome. EEG shows "slow" spike-and-wave at <2.5 Hz

IIa. Simple partial status epilepticus (also see IIb)

i. Frontal lobe simple partial NCSE with affective/cognitive features
ii. Parietal lobe simple partial status with somatosensory features
iii. Temporal lobe simple partial status with autonomic features
iv. Occipital lobe simple partial status with visual features, with or without nystagmus

IIb. Complex partial status epilepticus (CPSE)

i. Frontal lobe (FCPSE)
Fronto polar/fronto-central NCSE, with severe confusion and major behavioral disturbances (Supplementary motor, cingular, orbito-frontal, dorsolateral frontal lobe epilepsies exist, but localized status is rarely documented)
ii. Temporal lobe (TCPSE)
a) Mesial temporal lobe
1) Hippocampal or medial basal, limbic (experiential hallucinations; interpretative illusions)
2) Amygdalar or anterior polar amygdalar (nausea, fear, panic, olfactory hallucinations progressing to staring with oral/alimentary automatisms)
b) Lateral (neocortical) posterior temporal lobe with auditory or visual perceptual hallucinations progressing to disorientation, dysphasia and head movement (nystagmus; staring)
c) Opercular/insular with vestibular/autonomic hallucinations (progressing to staring and oral/alimentary automatisms)

III. NCSE presentation by age (some overlap with IA and B)

i. Neonatal NCSE
ii. Myoclonic-astatic epilepsy with AASE
iii. Electrical status epilepticus during slow sleep (ESES)
iv. Landau-Kleffner syndrome (acquired epileptic aphasia)
v. Minor epileptic status of Brett
vi. Rolandic status
vii. NCSE in the elderly (also see IAii)

(Continued)

Table 2 ***(Continued)***

IV.	**NCSE presentation with learning delay and mental retardation (some overlap with IA, B, III i–v)**
	i. In children
	ii. In adolescents
	iii. In adults
V.	**Electrographic status in coma**
	i. Subtle status, usually post convulsive status epilepticus (CSE)
	ii. With major CNS damage, often with multiorgan failure, (with facial, perioral and/or limb myoclonias), but without apparent preceding CSE
VI.	**Allied ictal states**
	i. Confusion with periodic lateralized epileptiform discharges (PLEDs) or PLEDs-plus
	ii. Confusion with bilateral independent periodic lateralized epileptiform discharges (BiPLEDs)
	iii. Confusion with bilateral synchronous epileptiform discharges (GPEDs)
	iv. Epileptic encephalopathies: altered mental status with disorganized diffuse or multifocal epileptiform features (e.g., with hypsarrhythmia; "interictal" severe Lennox-Gastaut syndrome; borderline NCSE vs triphasic wave toxic encephalopathies (lithium, baclofen, tiagabine)

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3. EEG DIAGNOSIS OF NCSE

A major challenge in definition has been the correct EEG identification of seizures. Because the determination of what represents seizures, and thus SE, on EEG depends on somewhat subjective interpretation, the art of diagnosis depends on accurate EEG interpretation. A universal EEG definition of seizure activity has been hard to pin down, as evidenced by the problems that even sophisticated, computerized seizure and spike detectors have had in correctly identifying seizures and distinguishing them from artifact. Some typical themes, however, can be noted. Seizures captured in their entirety will typically show a progression from low-voltage high-frequency spikes to high-voltage lower-frequency spike slow-wave activity before stopping abruptly and being replaced by background suppression. This progression from fast to slow components can be used to identify an isolated seizure. Problems arise, however, when the patient is in SE and activity thought to be epileptic precedes the beginning of the tracing and continues beyond the end of the tracing. In such cases, a rhythmicity, often with variability, typically faster than one-per-second is usually seen. Rhythmic activity may contain sharply contoured or spiky components, typical spike slow-wave or polyspike slow-wave complexes, or even rhythmic theta or delta frequencies. The major differential diagnostic confounders are epileptiform morphologies usually seen at less than one-per-second, such as periodic lateralized epileptiform discharges (PLEDs), bilateral independent periodic lateralized epileptiform discharges (BiPLEDs), or even bilateral synchronous epileptiform discharges (GPEDs), all of that may be seen in cortical hyperexcitable states that may follow seizures in a patient with a structural abnormality, or in

patients with encephalitis. These states representing cortical "irritability," even with a clinical correlate of diminished level of consciousness, have historically not been classified as *active* seizures. The electrical activity has been judged to be insufficiently *fast*, and to lack a more flagrant clinical correlate (such as clonic activity) to be "ictal" or epileptic. Nonetheless, this borderline is a "gray zone" because ictal activity may not particularly favor the motor cortex so as to produce clonic activity; conversely it may represent the end of the electroclinical continuum that follows convulsive status epilepticus *(20)*.

Toxic, metabolic, and infectious encephalopathies, benzodiazepine withdrawal states, and neuroleptic malignant and serotonin syndromes may all be associated with altered behavior and levels of consciousness, accompanied by an abnormal EEG, often with epileptiform features such as triphasic waves. In this way, these states resemble, and can be confused with, NCSE, even to the point of suppression of "ictal" triphasic-wave activity after intravenous benzodiazepines.

4. DIFFERENTIAL DIAGNOSIS

Differentiation of types of NCSE along clinical lines—for example, differentiating cases of CPSE from GNSE—can be problematic because of the marked overlap among the clinical characteristics of the different types of NCSE *(14–16,21–75)*. Such blurring of the lines can be seen in the many publications that provide clinical correlates to clearly identified focal or generalized nonconvulsive status. For example, historically, total unresponsiveness was said not to occur in absence status, but such patients have been noted. Impaired consciousness may be common to many types of NCSE, as may be fluctuation in the level of consciousness, bradyphrenia and bradykinesia, confusion, or even simple automatisms.

Nonetheless, some generalizations can be made regarding CPSE and ASE. Fear, aggressivity, irritability, and anxiety are seen more frequently with CPSE than with ASE *(40)*. Similarly, stereotyped, complex automatisms are also more frequent in CPSE *(40)*. Lip-smacking, other oroalimentary automatisms, lateralized limb automatisms, and dystonic posturing, eye deviation, and nystagmus are typical of CPSE *(36,40–42)*. In both CPSE and ASE, patients may be agitated, violent, and aggressive, and may experience hallucinations. The following sections delineate the behavioral features, emphasizing distinguishing characteristics.

Taking a step back, it may not be as important to characterize NCSE into ASE or CPSE, as it is to recognize NCSE at all. At Johns Hopkins Bayview Medical Center, where some 120 patients with NCSE have been identified over the past 18 yr, the diagnosis was frequently delayed or even missed *(38)*. Table 3 describes clinical examples with such scenarios. To state the obvious, the suspicion that NCSE is present must enter the mind to trigger a request for an EEG, enabling diagnosis. Although cases of NCSE may present initially on any floor of the hospital, there are particular presentations favoring the emergency room, intensive care units, and on neurology and psychiatry services. NCSE may resemble other disorders. Examples of some of these are given in Table 4 (*see also* Chapter 3).

Table 3
Clinical Examples in Which the Diagnosis of NCSE Was Missed or Delayed

Lethargy and confusion attributed to a postictal state
Ictal confusion mistaken for metabolic encephalopathy
Unresponsiveness and catalepsy presumed to be psychogenic
Obtundation thought to be due to alcohol or drug intoxication
Hallucinations and agitation mistaken for psychosis or delirium
Lethargy presumed secondary to hyperglycemia
Mutism attributed to aphasia
Laughing and crying ascribed to emotional lability

Experience at Johns Hopkins Bayview Medical Center, Baltimore, Maryland.
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Table 4
Differential Diagnosis of NCSE

Neurologic
Mitochrondrial encephalopathies
Transient global amnesia
Organic brain syndrome
Posttraumatic amnesia
Complex migraine
Vascular compromise—ischemic; inflammatory
Toxic/Metabolic
Toxic/metabolic encephalopathy
Alcohol, benzodiazepine withdrawal
Hypoglycemia
Hypercalcemia
Neuroleptic malignant syndrome
Serotonin syndrome
Drugs: lithium, baclofen, tricyclics, tiagabine
Epilepsy/Seizure-related
Typical absence status epilepticus
Atypical absence status epilepticus
Lennox-Gastaut syndrome with encephalopathy
Altered mental states with PLEDs/PEDs/BiPLEDs
Prolonged postictal confusion
Epileptic fugue states/poriomania
Interictal/postictal psychosis
Psychiatric
Acute psychotic reactions
Somatoform disorders
Disssociative conversion reactions
Malingering

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5. CLINICAL AND BEHAVIORAL CORRELATES OF NCSE

5.1. Typical Absence Status Epilepticus

Typical and atypical ASE have been described as petit mal status, minor epileptic status, spike-wave stupor, epileptic twilight state, prolonged epileptic twilight state, *absence continue*, epilepsia minoris continua, ictal psychosis, status pyknolepticus, and *état de mal a l'expression confusionnelle.*

Typical absence status epilepticus (TAS) may be recognized initially only in a minority of patients (19%) and is often misdiagnosed as CPSE, postictal confusion, depression, posttraumatic amnesia, hysterical behavior, schizophrenia, or toxic states *(43,45)*. Three-quarters of the cases appear before the age of 20 yr, and in a third, TAS heralds epilepsy *(45)*. The typical clinical features described in absence status epilepticus are given in Table 5.

TAS starts abruptly without warning. Typical features include perioral myoclonus, myoclonic eyelid twitching, mild to marked obtundation, bradyphrenia and bradykinesia, and confusion *(45)*. The change in responsiveness can be highly variable, an illustration of which is provided in Fig. 1 *(54)*. Verbal functioning is usually preserved, but there may be poverty of speech and monosyllabic answers. Amnesia is not invariably present, and many patients can describe their experiences as they go into and remain in ASE *(45)*. Such descriptions can be seen in the subsection "Experiential" in Table 5. The following are typical experiential accounts of TAS:

> Mild clouding: mind slows down, understands, but delay in formulating answers; central visual field vibrates; feels drunk; perioral myoclonus; mild clouding with lip twitching so intense that could not drink coffee; marked clouding with funny feeling, lip twitching and amnesia; mild clouding with dizziness, feeling not oneself, and difficulty communicating; gradual but marked clouding with feeling edgy, uncomfortable and worrying, increasing intensity, limb jerking and wanting to withdraw to a safe place; mild clouding; feeling muzzy headed, strange, slow and "not myself"; fluctuating mild clouding—unable to look after myself, drowsy and off work; jerking of eyes *(45)*.

Other vivid descriptions include:

> Mild clouding with slow communication, eyelid fluttering and spasm in neck; fluctuating mild to marked clouding with change in character, becoming extremely snappy with severe headache and frequent jerks of the arms; gradual marked clouding with tiredness, difficulty concentrating, able to hear but struggling to find the meaning; mild to marked clouding with drifting away, slowness of answers followed by amnesia; fluctuating mild to marked clouding, feeling disturbed, vague, uncooperative, slow speech with slurring, and occasional jerks with strange, disoriented behavior; marked clouding with confusion, in a trance, missing pieces of conversation and wandering; marked clouding, insomnolence with strange feeling, dizziness, increased confusion, purposeless walking around, repeating "yes" to questions and fumbling with clothes *(45)*.

Experiential descriptions are vivid. One patient describes seeing the world through a different medium, and of "not being there," "not being in the same world as everyone else" *(45)*. Other descriptions include a "feeling of uncontrollable rush of thoughts and fear of the loss of control of the mind." One patient

Table 5
Clinical Features Described in Absence Status Epilepticus

Attitude
Unreactivity to threat
Lack of initiative
Inability to plan
Withdrawal
Affect
Indifference
Perplexity
Crying
Laughing
Aggressivity
Memory/Cognition
Variable amnesia
Slow ideation
Disorientation
Speech
Verbal perseveration
Monosyllabic answers
Lack of spontaneous speech
Interrupted speech
Clicking noises in mouth
Motor
Hippus
Clumsy motor performance
Motor perseveration
Automatisms (chewing; compulsive handling of objects)
Rhythmic blinking
Eye rolling
Small amplitude jerking of face or arms
Quivering of lips
Tonic neck spasms
Ataxic gait/pseudoataxia
Wandering
Behavior
Inappropriate for situation with preserved alertness
Infantile behavior
Fugue states
Catatonia
Psychiatric
Hallucinations
Paranoid persecution
Experiential
Feeling of oppression
Uncontrollable rush of thoughts
Desire to (but inability to) perform simple motor acts (motor apraxias)

(Continued)

Table 5 ***(Continued)***

Dreamy state: "feels vague"
"In a different world"
"Drifting away"
"Drunk"
Worried; edgy
Dizzy
Missing pieces of conversation
Central vision "vibrates"
Other
Incontinence
Diarrhea
Headache
Frontal release signs
Babinski reflex

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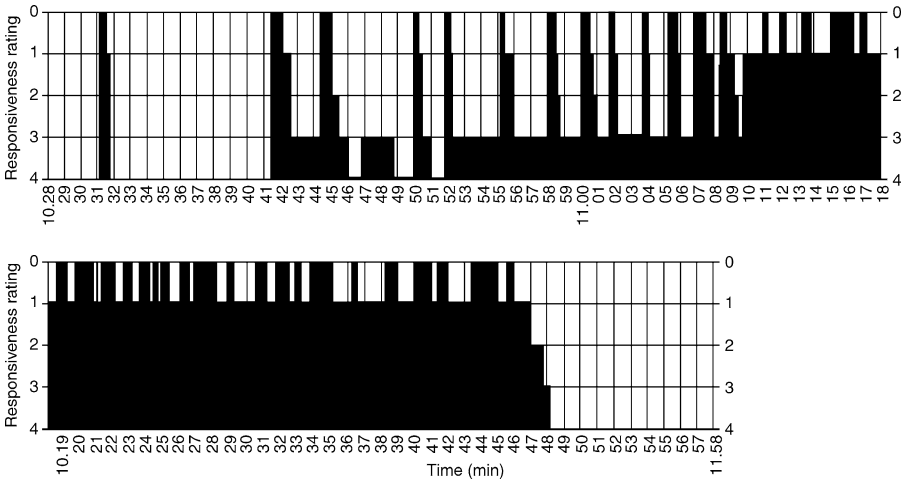

Fig. 1. Responsiveness during petit mal status. The patient has a brief absence attack at 10:31 AM, then a series of attacks beginning at 10:41 AM, with intervening periods of normal responsiveness. She had severe impairment of responsiveness from 11:10 to 11:48 AM, and then made a sudden recovery without postictal abnormality or complaint. The verbal responsiveness rating is as follows: 0, no response; 1, minimal response; 2, comprehension, follows simple directions, identifies receptively, cannot answer verbally, anomia may be present; 3, partial responsiveness, responds appropriately with one or two words and rote phrases, abnormal affect, some anomia; 4, accurate and immediate response, normal affect, responds to others' comments, and initiates conversation, responds with more than one response to others' comments, and inititates conversation, responds with more than one or two words (from ref. *54* with permission of the publisher, Baillière Tindal.)

described it as "like sitting in a movie"; another description is "as if one were walking through the water of a swimming pool to meet somebody." One patient was even able to look at a Walter Scott poem without turning the page and yet the next day was able to remember the entire page by heart, having never previously read the poem *(45)*.

The patient may complain of visual hallucinations, go into a dreamy state, and interact in a vague and inappropriate way. Patients may fail to recognize familiar people, and may appear introverted or frankly disoriented. One patient described a feeling of "closeness" or "heat" *(45)*. Other typical behavioral aberrations include a patient who went to bed with his coat and boots on; at work he could not open his locker and while turning the key complained that he could not get his truck started. This patient put two cups into an empty dishwasher and ran it without detergent, took out a cigarette and looked at it in a puzzled fashion, and after a shower was unable to get dressed *(76)*. Before and after NCSE, his ability to draw a clock face changed markedly (Fig. 2). Another patient made coffee twice and put trousers over his pajamas, and one got up in the middle of the night to tell his wife that he was driving to work and promptly drove into a stop sign *(45)*.

TAS may present with aggression, impulsive behavior, agitation, and hostility *(43,50)*. Some patients regress to infantile behavior, breaking dishes, scribbling on the walls, putting salt into coffee or milk in the sink, and insulting siblings. Some of this behavior is inappropriate rather than retrogressive *(42)*. One patient described by Andermann and Robb asked for a telephone number but then proceeded to give his own home address; another turned the water taps on and off *(43)*. Even amidst apparent confusion, some patients will retain much that takes place and be able to carry on relatively complex activities *(43)*.

Clouding of consciousness can obscure other more typical and, therefore, diagnostic clinical features. Dunne and colleagues *(39)* described some patients presenting with nausea, vomiting, headache, and visual disturbance, who were later found to be in absence status. Other autonomic symptoms include changes in heart rate and sweating.

As noted, differentiating TAS from CPSE (EEG aside) can be challenging. Some behavioral distinctions among absence, temporal lobe, CPSE, and frontal lobe CPSE are given in Table 6. Contrasting with CPSE, TAS typically induces little amnesia, and there is little postictal confusion after the event *(43)*. In TAS, there is usually little cycling between periods of unresponsiveness and partial responsiveness as may be seen in CPSE. Intellectual impairment is usually mild when compared with the severity of psychic symptoms *(43)*.

5.2. Atypical Absence Status Epilepticus

Atypical absence status epilepticus (AASE) has been described in patients with mental retardation and Lennox-Gastaut syndrome. In such patients, there may be no precise onset or offset of status, and the interictal state may merge with the ictal. This may produce relative changes in behavior, responsiveness, and attention, making such states particularly difficult to identify. Patients are said to have

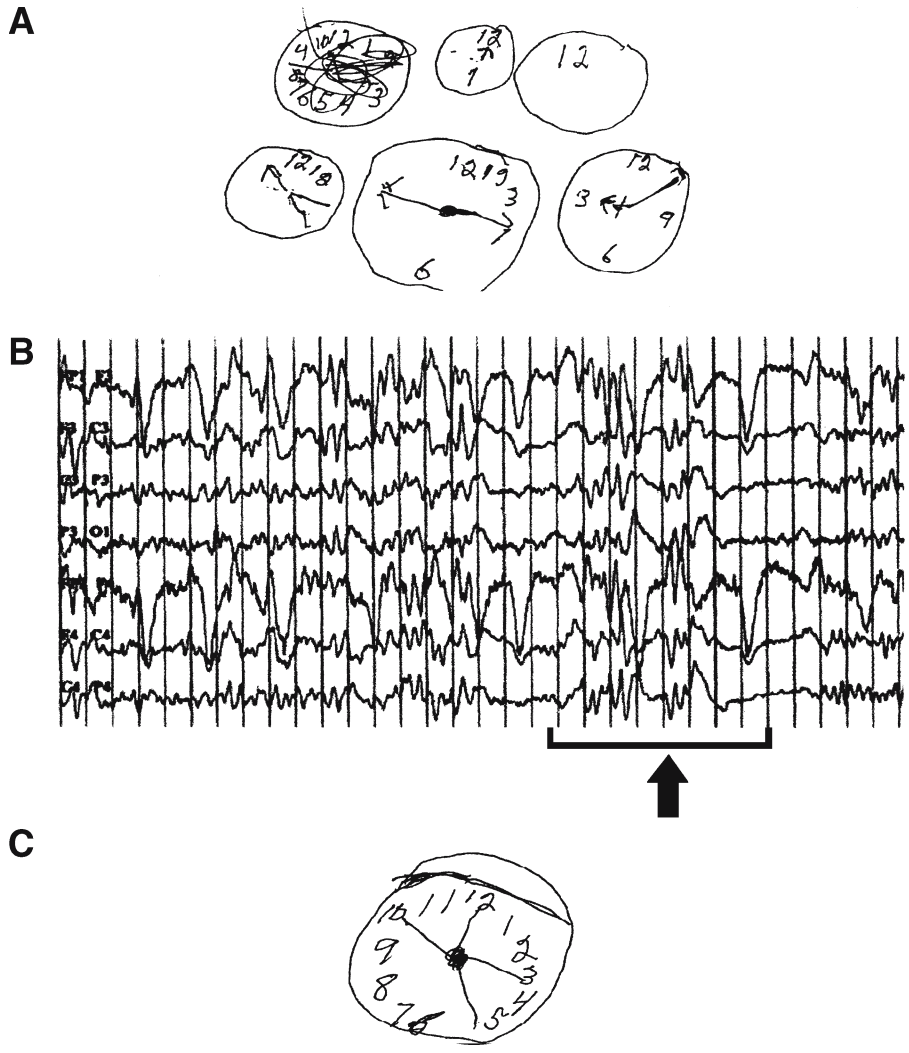

Fig. 2. (A) Patient's effort to draw the face of a clock during NCSE with EEG as seen in 2B. **(B)** EEG during NCSE showing runs of bilateral, synchronous polyspike-slow-wave complexes. **(C)** After treatment of NCSE with lorazepam, patient is able to draw a better clock. (Reprinted from ref. *76*; permission granted by American College of Physicians.)

"dysfunctional days" with level of consciousness particularly affected. Such changes in consciousness with AASE are given in Table 7. Unlike in TAS, convulsions rarely herald or terminate AASE. About 50% of patients may have perioral, facial, or limb myoclonus *(42,55)*. Further discussion on characteristics of AASE is in later paragraphs.

Table 6
Behavioral Distinctions Among Absence, Temporal Lobe Complex Partial, and Frontal Lobe Complex Partial Status Epilepticus

	ASE/AASE	TCPSE	FCPSE
Cognition			
Impaired consciouness	****	***	***
Fluctuating level of consciousness	****	**	**
Slowness	**	–	**
Verbal automatisms	–	*	–
Confabulation	–	–	*
Paranoia	–	**	–
Mood			
Indifferent; brooding	*	–	*
Puzzled; mute	*	–	**
Ironic	–	–	**
Smiling; laughing	–	–	**
Anxious; frightened	–	**	–
Angry	–	*	–
Aggressive; irritable		***	
Agitated	*	–	–
Movements			
Simple automatisms	*		
Complex automatisms	–	**	–
Wandering	–	*	–
Facial/global myoclonia	***	–	–

Percentage of affected cases:
– = <10%
* = 11–25%
** 26–50%
*** >50%, <90%
**** ≥90%

ASE, Absence status epilepticus; AASE, Atypical absence status epilepticus; TCPSE, Temporal lobe complex partial status epilepticus; FCPSE, Frontal lobe complex partial status epilepticus.

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5.3. Simple Partial Nonconvulsive Status Epilepticus

Simple partial nonconvulsive status epilepticus (SPNSE) may be difficult to prove (*see* also Chapter 7). Although subjective symptoms may be striking, the scalp EEG is frequently unrevealing. In effect, the argument is circular: Patients diagnosed as having SPNSE *must* have an EEG correlate. Depending on the particular brain region involved, the symptoms differ *(7,56–59)*. Autonomic and vegetative features may appear, including ictal fear, anorexia, weight loss *(56)*, and poorly described visceral sensations *(7)*. There may be mild confusion, bad-tempered behavior,

Table 7
Alteration of Consciousness as a Manifestation of Atypical Absence Status Epilepticus

A. Slight clouding	19%
Slowing of expression	
B. Marked clouding	64%
Mutism	
Immobility	
Delay in response	
Marked disorientation	
Islands of memory	
Automatisms	
C. Somnolence	7%
Severe immobility	
Eyes closed, upward	
Staggering	
Incontinence	
D. Lethargy	8%
Epileptic stupor	
Reacts to painful stimulation	
Incontinence	

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depression, or even suicidal ideation with an anterior temporal focus *(57)*. A temporal focus may also engender inchoate fright *(58)*. More posterior ictal foci in the temporo-parieto-occipital junction may induce adversive eye movements with stepwise contraversive nystagmus *(59)*. Right-hemisphere SE may be barely perceptible by clinical examination, and only identified by careful neuropsychologic testing *(60)*. Occipital simple partial seizures can induce macropsia (distortion of increased size) or micropsia (the inverse), misperception of spatial orientation, hallucinations of animals, movie scenarios, or simple patterns of color and light *(61)*. Transient cortical blindness may occur *(62)*. Although simple partial SE is frequently presumed in the absence of EEG evidence, all published cases are supported by an EEG correlate *(7)*.

5.4. Complex Partial Status Epilepticus

The first case of CPSE was probably described by Gastaut and Roger in 1956 *(9)*, but by 1985 only 17 clearly identified cases had been published *(37)*. However, with increasing use of video EEG recording, hundreds of cases have been identified since *(63,64)*. Nonetheless, it is probably an underrecognized entity *(30,63)*. Other terms used to describe CPSE include temporal lobe status epilepticus, prolonged epileptic fugue, psychomotor status epilepticus, prolonged epileptic twilight state, or even poriomania *(17,18,22,23,25,37,65)*.

CPSE can broadly be described as abnormal behavior or level of consciousness associated with lateralized seizure activity, with impairment of consciousness rang-

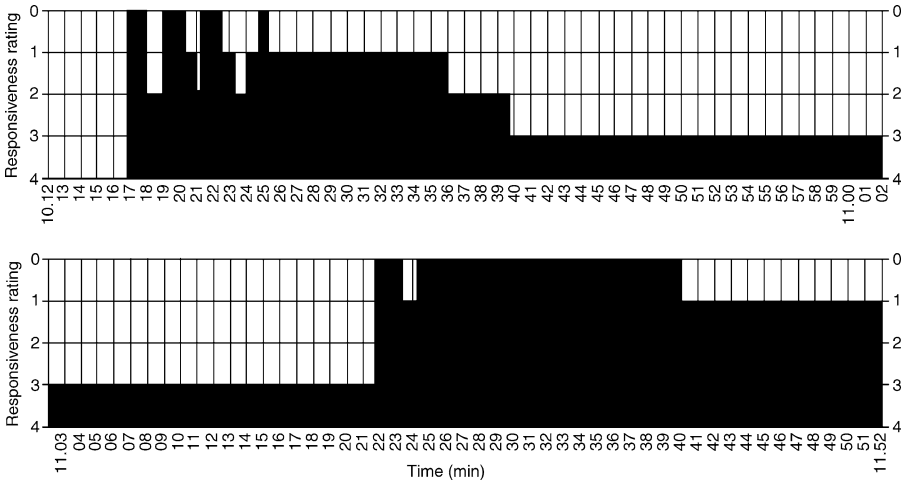

Fig. 3. Responsiveness during complex partial status. The patient had a complex partial seizure at 10:17 AM and did not recover normal consciousness until several hours later. He had several attacks at the onset of status (10:17 to 10:25 AM), then appeared to be gradually recovering, but had another series of attacks beginning at 11:22 AM. Recovery occurred gradually. The responsiveness rating is the same as in Fig. 1 (Reprinted from ref. *54* with permission of the publisher, Baillière Tindall.)

ing from almost nondiscernible clouding of certain higher cortical functions, to coma. Arguably, the comatose cases associated with electrographic seizure activity represent a different disease with different etiologies, management decisions, and prognoses. These cases probably constitute a condition in which severe brain damage or medical illness is associated with seizure activity as an epiphenomenon *(30,66)*.

Table 6 illustrates the great variability in clinical correlate with CPSE from changes in affect, "ironic smiles," Wernicke's aphasia *(67)*, or even fugue states. The typical marked changes in level of responsiveness over time are characterized in Fig. 3.

Although early descriptions differentiated CPSE from ASE with as simple a characteristic as a cycling or fluctuating presentation with CPSE versus continuous disturbances with ASE *(36,44,46,57,68)*, both cycling and continuous clinical presentations have been described with ASE *(36,40–42)*, requiring other clinical characteristics for a clear clinical differentiation. With the more than 200 cases described since the 1990s, clinicians have come to recognize the great variety of seizures and clinical presentations—"almost as many types as there are types of complex partial seizures." Hippocampal, amygdalar, and amygdalohippocampal CPSE often present with cyclical changes in behavior. Treiman and colleagues, reviewing 15 cases, noted a twilight state with partial responsiveness, intermittent speech arrest, and complex reactive automatisms *(68,71)*. Some patients were totally unresponsive, with motionless staring; others had alimentary automatisms, vocalizations, and perseverative gesticulations *(68)*.

Other examples of CPSE with temporal lobe predominance can nonetheless *originate* in the frontal lobes, with initial behavioral features representing frontal lobe dysfunction. Opercular, frontal lobe, and occipital-hippocampal regions can all spread secondarily to involve mesial temporal regions *(68)*. Extratemporal foci may produce vestibular hallucinations, unilateral arm automatisms, and visual illusions, although when involving the amygdala and hippocampus, there typically will be chewing movements, lip-smacking, and gesticulatory automatisms *(68)*. Other extratemporal clinical features may include somesthetic hallucinations, a perception of warmth, pupillary changes, changes in facial color, nausea, tonic posturing of the arm, or auditory hallucinations *(68)*. In occipital involvement, scotomata or simple visual hallucinations predominating in the central visual field may occur. Slightly more anteriorly, involvement of the temporo-parieto-occipital junction may induce nystagmus with contraversive eye deviation *(59)*. Even more anterior localization or spread through the temporal lobe may induce postural changes of the limbs or even bizarre limb automatisms, changes in head position, wandering, or a "fencing" posture. Contrasting with TAS, CPSE patients may be totally unresponsive *(68)*. Williamson describes a patient studied with depth electrodes who clinically manifested verbal unresponsiveness, confusion, and head and eye deviation, and yet localization lay in the hippocampus *(64)*. Another example included a patient with head deviation, arm stiffening, and mutism, but with preserved alertness, with a supplementary motor area origin but subsequent evolution to CPSE and unresponsiveness *(64)*.

5.4.1. Frontal Lobe CPSE

With increasing understanding and enhanced delineation of electroclinical types of NCSE, a more anterior localization for CPSE was identified. Foci were seen to arise from one or both frontal regions, with original descriptions entitled, "petit mal status-like . . ." or "borderline petit mal status" or "transitional petit mal status" *(16,22,23)*. Other terms have been "absence status with focal characteristics," "acute prolonged confusion as a frontal-onset ictal state," "prolonged cyclic epileptic seizures," "nonconvulsive confusional frontal status," "acute confusional states with frontal origin," "frontal status," and "CPSE of frontal origin" *(16,22,23,60,72–75)*. Work by Rohr-le-Floch and colleagues *(40)* and Thomas and colleagues *(25)* have revealed more of the subtle differences distinguishing frontal CPSE from ASE (Table 6).

With frontal lobe CPSE (FLCPSE), there is generally a lesser impairment of consciousness, and fewer fluctuations *(40)*. Patients may confabulate, have an "ironic" appearance, inappropriate laughter and smiling. Patients may appear indifferent or brooding—all characteristics less commonly seen with temporal lobe CPSE (TLCPSE). Less frequently, fear, anxiety, anger, irritability, negativism, aggressiveness, agitation, and simple and complex automatisms were seen; these were more common with TLCPSE, as was psychomotor slowing *(40)*.

Unfortunately, such careful differentiation of CPSE into frontal and temporal types is rarely explored in the many large series of patients published with NCSE. Thomas

and colleagues delineated two types of frontal NCSE: type one had affective disinhibition or indifference, subtle impairment of cognition and mood disturbances, but with no overt confusion *(25)*. EEG showed a unilateral frontal focus. Detailed descriptions include patients able to carry out activities of daily living, such as eating, dressing, washing, walking, and orientation to name, age, address, and telephone number. Complex tasks, such as subtracting serial 7s, reproducing alternative sequences of pattern, or putting a sheet of paper in an envelope, were associated with bradyphrenia, perseveration, and impaired concentration. Other affective and behavioral impairment included disinhibition, affective indifference or overfamiliarity, and mild hypomania *(25)*. Patients were noted at times to have a blank facial expression, lack of spontaneous emotion, and decreased verbal fluency *(25)*. Fluctuations in these correlates were noted. Some patients had head or eye deviation, low-amplitude jerks of the mouth, or simple automatisms such as scratching, rubbing, or picking at clothes. Most patients were not amnestic. The more "typical" frontal lobe seizure features, such as pedaling or "fishing," were absent. Thomas and colleagues emphasize that it is the "mood disturbance" rather than a "confusional state" that best describes these conditions *(25)*.

FLCPSE can be particularly difficult to separate from TAS, and some believe that the appearance of generalized activity actually stems from a unilateral frontal focus by secondary bilateral synchrony *(77,78)*. As noted by Thomas and colleagues, no subjective or objective cognitive sequelae were seen after type one FLCPSE.

The rarer type two FLCPSE had greater impairment of consciousness associated with bilateral frontal foci *(25)*. There were marked behavioral disturbances, temporospatial disorientation, confusion, and perseveration. Patients were clearly distractible and showed cyclic fluctuations even to the point of requiring restraints for aggressiveness. Perioral myoclonia were noted and in one patient ended with a broad smile. Others exhibited catatonic stupor with only simple gestural automatisms. Patients were universally amnestic for the episode *(25)*.

5.5. NCSE Presenting in Infancy, Childhood, and the Elderly

Neonatal nonconvulsive status epilepticus differs from its clinical expression at other ages (*see* Chapter 17). Premature and term infants may show only mild facial and limb jerking, eye deviation, eyelid fluttering, apnea, or autonomic changes with movement suggestive of rowing, pedaling, swimming, or boxing *(7)*. Seizures lasting for days may be correlated with high-voltage slow EEG activity, rhythmic activity, or burst suppression. Some electrographic seizures have no clinical correlate. TAS or CPSE, properly speaking, do not occur. Infantile epileptic encephalopathy (EIEE) or Ohtahara's syndrome typically presents with greater flexor, extensor, or tonic spasms *(7)*. In the setting of West syndrome, diagnosis may be difficult because of the underlying encephalopathy and fluctuations in clinical state. In mildly retarded patients, there may be interruption of visual contact and decrease in affective components, particularly with hypsarrhythmia. Oral automatisms, eye blinking, hypersalivation, and apathy are described *(7)*. Typical clinical features of NCSE in infants and children are given in Table 8.

Table 8
Clinical Features of NCSE in Infants and Children

Apathy
Absentmindedness
Pseudodementia; stupor
Decreased alertness, cooperativeness or "chattiness"
Restlessness
Aggressiveness
Mutism; inappropriate verbal outbursts
Ataxic spells; falls
Decreased affective or visual contact
Increased salivation
Eye blinking; blank expression; staring`
Oral automatisms
Perioral, facial, and limb twitching
Shivering
Regressive or infantile behavior in older children
Head nodding

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With myoclonic-astatic epilepsy, SE presents with apathy, ranging to stupor. There may be facial muscle twitching, twitching of the limbs, salivation, blank facial expression, and dysarthric speech *(7)*. Lasting hours to weeks and often varying with sleep-wake cycles, SE may occur shortly after awakening, with patients lying obtunded in bed. With Lennox-Gastaut syndrome, or secondary generalized myoclonic-astatic epilepsy, there may be stupor, atonic spells, head nodding, myoclonic jerks, and myoclonias of the face *(7)*.

NCSE in children with normal intelligence is rare but occasionally occurs with benign Rolandic epilepsy, in which there are speech arrest, drooling, problems with swallowing, weakness of the face, head deviation, and mild confusion *(79–81)*. Nonconvulsive states may also occur over the occipital regions, with nausea, anorexia, and visual hallucinations.

5.6. NCSE in the Developmentally Delayed

Electrical status epilepticus during slow-wave sleep (ESES) typically occurs in mentally retarded children, with a nocturnal expression (*see* also Chapter 16). Characteristic spike-wave discharges occur during at least 85% of non-REM sleep *(7)*, with seizures appearing between ages 1 and 14 yr. IQ usually ranges from 45 to 80, with hyperkinetic and aggressive behavior, memory impairment, and psychosis *(7)*. Language eventually regresses to mutism. A similar disorder, Landau-Kleffner syndrome, has fewer non-REM spike-waves, and a different pattern of psychological impairment *(82,83)*. It is not known whether the EEG is an epiphenomenon of the encephalopathy or the electrical activity itself is responsible for regression and brain damage. Landau-Kleffner syndrome usually supervenes in children with a previously normal development, between the ages of 2 and 4 yr. There is a gradual

deterioration in language, with expressive aphasia, auditory agnosia, word deafness, and impaired speech output. Curiously, the EEG focus may be in the nondominant hemisphere. Along with speech problems, intellectual problems, hyperkinetic behavior, and personality disorders occur *(7)*.

Children and adolescents with mental retardation and learning difficulties may also be difficult to diagnose. Patients may lose their "chattiness," "cooperativeness," and degree of participation in ongoing activities *(14)*. From the behavioral perspective, the patients appear to have frontal lobe seizures, although the EEG localization interictally is more variable *(14)*. Most patients appear to have either Lennox-Gastaut syndrome or Landau-Kleffner syndrome *(14)*. During later childhood, one can recognize the more classic clinical presentations of NCSE in the form of AASE and CPSE, as described above. Stores provides typical descriptions such as:

> "stares vacantly ahead, dribbling, answers questions very slowly, speech very slow and deliberate"; "some days he switches off"; "has period of appearing deaf and blind"; "sluggish, uncooperative and drowsy" *(20)*.

The patient may bump into objects, walk into doors, and exhibit poor balance, poor control of movements, and frequent falls *(20)*. These clinical features have been referred to as *pseudodementia* and *pseudoataxia*. Clinical features are provided in Table 9.

Ring chromosome 20 with NCSE has been delineated in patients from Japan between the ages of 13 and 31 yr *(84)*. Seizures are characterized by intercurrent motor seizures with a prolonged confusional state, staring, head turning, mutism and meaningless utterances, facial flushing, and shaking of the arms and legs. Impulsive behavior, aimless walking, inappropriate responses, mutism, and eyelid and extremity myoclonia were described during episodes that could occur several times daily.

5.7. NCSE in Adults With Mental Retardation

NCSE in adults with mental retardation also presents diagnostic challenges, predominantly colored by the baseline neurologic state of the patient. Particularly with mentally retarded patients with behavioral problems interictally, ictal changes may not be noted. Some examples, however, are: "apathetic for several days; staring vacantly into the air, appeared almost comatose"; "responded after a considerable delay"; "extremely stubborn and would not eat or find the toilet"; "had slight perioral tremor and irregular twitching"; "refused washing"; "had episodes of faintness with empty staring and perioral movements"; "unintelligible verbal outbursts"; "inappropriate undressing and repeated maneuvers such as making coffee"; "generalized shivering." All patients had Lennox-Gastaut syndrome *(15)*. With such patients, psychiatric features may predominate, suggesting a psychiatric problem rather than NCSE. A typical feature is one of "regressive behavior" compared with the patient's baseline, and there may be degrees of obtundation that point to NCSE *(15)*.

5.8. NCSE in the Elderly

NCSE in the elderly, delineated by Thomas and colleagues, usually affects a different patient substrate *(21,85–88)*. It occurs in the setting of metabolic dysfunction,

Table 9
Clinical Features of NCSE Described in Mental Retardation

Attitudinal
Stubbornness
Aggressiveness
Passivity
Absentmindedness
Level of consciousness
Unresponsiveness
Drowsiness
Confusion
Coma
Speech
Mutism
Perseveration
Motor
Tremor
Perioral, facial, limb movements
Myoclonic jerks
Restlessness
Shivering
Constitutional/regressive or vegetative
Anorexia
Decreased eating and drinking
Vomiting
Bedwetting

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intercurrent infections, and cerebral atrophy, and the clinical state may be attributed to other causes of delirium and stupor. Diagnosis may be delayed for up to 5 d *(21)*. Morbidity and mortality may reach almost 60% *(85–88)*. Clinical correlates included "interrupted speech, catatonia, slow and ataxic gait." Chewing and compulsive handling of objects, frontal release signs, and Babinski reflexes have been reported. Almost three quarters of patients above the age of 40 are women *(87,88)*, with typical triggers including drug withdrawal, toxic or metabolic dysfunction, and the use of neuroleptic, psychotropic medications, particularly the benzodiazepines. Two thirds have moderate impairment of consciousness with unresponsiveness, staring and waxy rigidity, severe language problems to the point of mutism, and verbal perseveration *(88)*. The patient may be agitated, aggressive, hallucinating, and emotionally labile. Frequent minor motor accompaniments are twitching of the eyelids, mouth, and limbs *(88)*.

6. CONCLUSION

It has been 50 yr since a clear EEG correlation to nonconvulsive SE was first made, leading to an ever-increasing understanding of the highly variable behavioral

and clinical correlates. A great variety of human cortical functions can be impaired to variable degrees in individual cases. NCSE can affect attitude, affect, memory, thinking, behavior, and level of consciousness.

NCSE is underrecognized and underdiagnosed, often with marked delays in requesting the EEG, and hence in making a diagnosis. Many of the features of NCSE have been attributed to other disorders, not the least of which were psychogenic. With clinical vigilance, the availability of EEG, and a knowledge of the pleomorphic clinical presentations, physicians should be able to diagnose and manage the great clinical and EEG spectrum of these diseases.

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11

Cognitive Manifestations of Status Epilepticus

Ictal Aphasia, Amnesia, and Psychosis

Michael Benatar

1. INTRODUCTION

Seizures are defined by the presence of abnormal synchronous neuronal activity; their clinical manifestations are determined by the specific anatomic location as well as the spatial and temporal propagation of this aberrant electrical activity. Seizures involving the motor cortex are perhaps most easily recognized, but seizure activity may also arise from or involve regions of cortex devoted to cognitive function. The term *nonconvulsive seizure* has been used, in part, to refer to seizures of this sort. This chapter is devoted to the cognitive manifestations of nonconvulsive seizure activity.

Traditionally, seizures are defined as either partial or generalized depending on whether the ictal activity begins focally (partial seizures) or involves both hemispheres diffusely from the outset (generalized seizures). Partial seizures are further classified as either simple or complex, depending on whether there is accompanying impairment of consciousness. Focal motor seizures are perhaps the simplest to understand. Seizure activity restricted to the motor cortex produces abnormal (tonic or clonic) motor activity and is regarded as a simple partial seizure. If there is accompanying impairment of consciousness, then the seizure is classified as being of the complex partial variety. The transient impairment of motor function that follows a seizure is known as Todd's paralysis. In the same way that seizures arising in the motor cortex manifest with abnormal motor function, seizure activity arising from, or spreading to involve, regions of the cortex that are devoted to specific cognitive function such as language or memory may result in selective dysfunction of the relevant cognitive modality. Selected cognitive dysfunction may similarly follow a seizure as a postictal phenomenon, analogous to Todd's paralysis.

As with other seizure types, nonconvulsive seizures may be partial or generalized. Generalized nonconvulsive seizure activity tends to produce a diffuse disturbance of cognitive function that may range in severity from mild encephalopathy to profound coma. Partial nonconvulsive seizures, on the other hand, may result in selective cognitive impairment, with the specific cognitive deficit being determined by the region

From: *Current Clinical Neurology: Status Epilepticus: A Clinical Perspective*
Edited by: F. W. Drislane © Humana Press Inc., Totowa, NJ

of cortex involved. This chapter focuses on the cognitive manifestations of partial nonconvulsive seizures.

When cognitive function is affected by a partial seizure, the distinction between simple and complex partial seizures, as well as the distinction between complex partial and generalized seizures, may not be so straightforward. These difficulties arise, in part, because a clinically useful definition of consciousness has proven somewhat elusive, and the routine clinical determination that consciousness has been impaired may often hinge simply on the degree of verbal responsiveness or the ability of the patient to recall the events that transpired during the ictus. Because focal impairment of language function and memory may interfere with these activities, it is not clear how best to classify such seizures. The second complicating factor is that it is often difficult to be confident of the specific nature of the cognitive deficit that occurs as part of a nonconvulsive seizure, especially if careful and detailed cognitive testing is not performed during the ictus. In the absence of such testing, it may be impossible to differentiate the global disturbance of cognitive function (i.e., encephalopathy) that accompanies generalized nonconvulsive seizures from a focal aphasic or amnestic deficit that is due to partial nonconvulsive seizure activity. Use of the term "impairment of consciousness" under such circumstances is too loose and is problematic because it masks the diversity of the cognitive manifestations of focal seizure activity.

A wide range of cognitive deficits has been described as a consequence of focal seizure activity (Table 1). Perhaps because focal seizures most commonly arise from the temporal lobe, abnormal language and memory function, as well as psychosis, are the most discussed and best understood. This chapter, therefore, is devoted to a discussion of ictal aphasia, ictal amnesia, and ictal psychosis.

Finally, the literature on focal cognitive dysfunction explicitly due to status epilepticus (SE) is quite limited. For the purposes of understanding the spectrum of cognitive disturbances that may result from seizures, it seems reasonable to suppose that the temporary cognitive manifestations of short-lived seizures would likely become more persistent if the seizures were ongoing. Furthermore, since the term *status epilepticus* implies either ongoing prolonged seizure activity or recurrent seizure activity with incomplete recovery between seizures, it is relevant to examine the cognitive effects that occur either as an ictal or a postictal manifestation. Thus, although this is a book about SE, this chapter will examine the cognitive manifestations of the postictal period as well as those of seizures in general.

2. ICTAL APHASIA

2.1. Introduction

The term *aphasia* is used to describe primary language dysfunction. An abnormality of speech is often the first clue to the presence of an aphasia, but it is important to recognize that not every speech disorder represents an underlying language disorder. The individual who fails to speak because he is comatose, for example, is not regarded as aphasic. In the awake individual, aphasia may be recognized by evidence of disruption of some facet of language other than speech. Examples include

Table 1
Cognitive and Behavioral Manifestations of Nonconvulsive Seizures

Cognitive/Behavioral Feature	Definition	Reference
Asomatognosia	Failure to recognize a body part as being one's own	*41,42*
Anosognosia	Lack of awareness of a neurologic deficit despite attempts to bring the deficit to the attention of the affected individual	*21*
Alien-limb	Limb performs seemingly purposeful actions that are subjectively experienced as unwanted and beyond the patient's voluntary control	*42*
Catatonia	Marked decrease in reactivity to the environment	*43*
Agraphia[a]	Impaired writing	*44,45*
Acalculia[a]	Impaired calculation	*45*
Left-right confusion[a]	Uncertainty regarding which side is right and which is left	*45*
Finger agnosia[a]	Inability to recognize and name individual fingers	*45*
Apraxia	Impairment of a learned motor task in the absence of an underlying motor, sensory or other cognitive defect	*45*
Echolalia	Inappropriate repetition of verbal stimuli (words, phrases and/or full sentences)	*46*

[a]Described in the context of Gerstmann's syndrome in a single patient.

the inability to name objects, impaired ability to repeat language via speech or writing, abnormal comprehension, evidence of disturbed syntax or grammar, or the presence of semantic or phonemic paraphasic errors.

There are a variety of ictal disturbances of speech, only some of which indicate an underlying aphasia. The spectrum of expressive speech disorders includes speech arrest or mutism, dysarthria (impaired articulation of speech), and abnormal vocalization (groans, moans, etc.). While dysarthria and abnormal vocalization may occur in conjunction with aphasia, they typically do not lead to confusion about the presence or absence of an associated language disorder. Speech arrest, however, has many causes, of which aphasia is only one. Speech arrest can also arise from dysfunction of the motor areas responsible for control of the lips, tongue and jaw or from an apraxia that involves the same structures. This may be one of the underlying mechanisms of speech arrest in children with benign Rolandic epilepsy *(1)*. To ascertain that speech arrest indicates an underlying aphasia, it is necessary to show normal buccofacial strength and praxis and to find other evidence of language dysfunction. Similarly, not every defect in understanding represents a primary disturbance of language comprehension. For example, reduced level of arousal or attention may interfere with the ability to understand, but this is not appropriately regarded as aphasia.

Given the requirement for preserved consciousness before aphasia is diagnosed, ictal aphasia can be confirmed only reliably during a simple partial seizure.

2.2. Clinical Manifestations of Ictal Aphasia

The gold standard for making the determination that an aphasia is ictal (i.e., epileptic) in origin is the presence of an electroencephalographic (EEG) recording that demonstrates seizure activity. Less definitive, but clinically more useful features are the presence of other ictal features such as tonic or clonic motor activity or the sequential development of ictal manifestations such as déjà vu, olfactory or gustatory hallucinations or secondary generalization. In the absence of an EEG, however, it is necessary to rely on the clinical manifestations of ictal aphasia.

Many of the early reports of ictal aphasia *(2–4)* do not help to elucidate their clinical features because the results of detailed language testing are not provided. There are only a handful of well-described cases of ictal aphasia in the literature. This may be, in part, because this is an uncommon clinical entity, but there are a variety of reasons for failing to recognize the presence of ictal aphasia that may contribute to underreporting. For example, if the subject is asleep or if no effort is made to speak, read or write during a seizure arising from the relevant brain region, then there may be no outward aphasic manifestation of the seizure. A related difficulty that may lead to under-recognition of ictal aphasia is the presence of more striking motor activity so that no effort is made to speak or to formally evaluate language function during the seizure. These concerns have implications for any attempt to determine the incidence or frequency of ictal aphasia.

Details of the reported cases of ictal aphasia are summarized in Table 2. Where possible, the aphasia has been designated Broca's, Wernicke's, mixed, or transcortical. Where the features suggest Broca's or Wernicke's, but the ability to repeat is not recorded, the designations 'anterior' and 'posterior' have been used. In a significant number of these cases, the aphasia was due to underlying status epilepticus. Gilmore and Heilman's report highlights an important issue *(5)*: Their patient presented with episodes of speech arrest, and they used a syntactic comprehension test to identify an underlying language disorder. This test examines the ability of a subject to distinguish the direct and indirect objects of a sentence, a task that requires an understanding of semantics (word order, inflections, etc.) in addition to lexicography (nouns, verbs, adjectives, etc.). Patients with anterior or Broca's aphasia have impaired semantic comprehension. For example, preserved semantic comprehension is necessary to understand the different meaning of the sentences "the man showed her baby the pictures" and "the man showed her the baby pictures." The frequent semantic errors their patient made when asked to point to pictures requiring differentiation of direct and indirect object relationships provides evidence for an underlying disturbance of language in the face of a complete absence of speech production (i.e., speech arrest or mutism).

A few conclusions may be drawn from these case reports. First, virtually every type of aphasia may occur as an ictal manifestation. Second, seizures do not seem to largely produce any single type of aphasia. Third, there is no characteristic feature

Table 2
Clinical Features of Individual Cases of Ictal Aphasia With Associated Clinical and EEG Characteristics

Reference	Type of aphasia	Other ictal features	Ictal EEG	Response to AEDs
Rosenbaum *(47)*	Broca	Right hemiparesis and numbness; clonicmovements of jaw and right hand	L centroparietal rhythmic activity 12 Hz	Not reported
Hamilton *(48)*	**Anterior**	Right facial weakness	Paroxysmal L frontal and anterior activity	No speech recovery between EEG bursts of seizure activity
Wells *(49)*	**Mixed**	Mild right pronator drift	L rhythmic 14 Hz sharp waves	Abrupt response
Kirshner *(50)*	**Transcortical sensory**	Acalculia	Frequent L temporal ictal activity	Gradual improvement
Knight *(51)*	Wernicke	None	Bursts of L temporal poly-spike and slow wave	Gradual improvement
Racy *(52)*	Mixed	None	L temporal delta and sharp waves	Gradual improvement
Racy *(52)*	Posterior	None	Continuous ½–1 Hz L temporal sharp waves	Not reported
Dinner *(53)*	**Mixed**	None	Bursts of L temporal 11–12 Hz sharp activity	Gradual improvement
Doody *(54)*	Wernicke	None	Pseudoperiodic L temporal 1–3 Hz spike and slow waves	Not reported
de Pasquet *(55)*	**Wernicke**	Single clonic seizure of right arm	L fronto-temporal 6–7 Hz activity	Mild persistent aphasia

(continued)

Table 2 ***(Continued)***

Reference	Type of aphasia	Other ictal features	Ictal EEG	Response to AEDs
Grimes *(17)*	**Mixed**	Rightward gaze	L temporal seizures	Abrupt response
Suzuki *(56)*	Mixed	Sometimes followed by arousal	L fusiform gyrus seizures	Not reported
Abou-Khalil *(57)*	Mixed	Olfactory hallucinations	L temporal ictal discharges	Not reported
Primavera *(58)*	Global	None	Rapid low voltage activity, then spikes and then slowing	Gradual improvement
Spatt *(59)*	**Global**	Simple auditory hallucinations	Paroxysmal L temporal sharp activity	Gradual improvement
Murchison *(60)*	**Wernicke/ Global**	None	Runs of high amplitude irregular activity	Abrupt response
Gilmore *(5)*	Broca	Mild right facial, orobuccal, and hand apraxia	L frontocentral and temporal ictal discharges	Abrupt response

Bold font indicates that aphasia was due to status epilepticus.
L, left; R, right; AED, antiepileptic drug.

of an ictal aphasia that could be used to distinguish it from aphasia due to other pathology. It was only in a minority of cases that there was other evidence of seizure activity (e.g., clonic limb movements, olfactory hallucinations, impaired consciousness following the aphasia) that indicated the epileptic nature of the aphasia. Fourth, the correlation between the location of the ictal activity and the nature of the aphasia is not straightforward. For example, there is no clear tendency for Wernicke type aphasias to result from more posteriorly located ictal discharges. Finally, underlying structural pathology could be demonstrated in the majority of cases.

2.3. Postictal Aphasia

With few exceptions *(6)*, the literature concerning postictal aphasia is difficult to interpret because of the frequency with which a designation of aphasia is made in the absence of a detailed assessment of language function *(7–9)*. Language evaluation was incomplete even in one of the more careful studies of postictal aphasia in which the authors used a nonstandardized protocol to examine naming, execution of simple verbal commands, and reading *(10)*. In this study of 31 patients, 12 were classified as aphasic, with most showing features of both expressive and receptive dysfunction. All these patients had a temporal lobe focus; in nine patients the focus was in the dominant hemisphere and the remaining three patients had bilateral speech representation (defined by the results of Wada testing). Onset and spread of seizure activity was examined with intracerebral electrodes in six patients with postictal aphasia (all with left hemisphere dominance) and nine nonaphasic patients. The results indicated that postictal aphasia occurred only when the seizure focus was in the dominant hemisphere and when seizure activity propagated widely to involve language areas in the ipsilateral hemisphere.

2.4. Landau-Kleffner Syndrome

A chapter dealing with ictal aphasia would be incomplete without reference to an entity described by Landau and Kleffner as a syndrome of acquired aphasia with convulsive disorder in children *(11)*. This is a syndrome in which a language disorder is thought to be caused directly by epileptic discharges in regions of the brain that are critical for normal language function. The boundaries of the syndrome are not well defined. However, the typical story is that of a child with normal early language development, who shows signs of regression of already-acquired linguistic skills between the ages of 3 and 7. Onset may be abrupt or insidious and the degree of language impairment may fluctuate. Initially, comprehension is more severely affected, but with time there is a gradual decline in verbal output too. Clinically overt seizures are uncommon. The waking EEG is normal, and the key finding in this syndrome is the presence of very frequent spike-and-wave discharges in the sleep EEG. The topography, abundance, and persistence of the spike-and-wave discharges are variable between patients and at different stages of the syndrome. At some time, all patients will exhibit bilateral spike waves for the majority of the sleep period—the so-called continuous spike waves during slow wave sleep (CSWS). Corticosteroids are usually more effective than traditional antiepileptic drugs in the treatment of both

the clinical and EEG abnormalities. Outcome is variable. Some children recover completely, but others remain with permanent severe aphasia.

It is difficult to draw comparisons between the effects of epileptic activity in the language areas of the developing brain of the child and in the mature adult brain. This syndrome, however, serves as a model for the relationship between epilepsy and language, and exemplifies the concept that prolonged language dysfunction may result from persistent epileptic activity in the relevant brain regions.

2.5. Conclusions

The available evidence suggests that seizures may disturb language in many different ways and that there is no typical profile to ictal aphasia. Furthermore, ictal aphasia may occur as an isolated manifestation without other evidence of seizure activity. When faced clinically with the problem of an isolated aphasia without other evidence to indicate a stroke, space-occupying lesion or seizure, it may not be possible to distinguish these possibilities without further investigation.

3. ICTAL AMNESIA

3.1. Introduction

The relationship between seizures and memory dysfunction is a complex one. In trying to unravel these complexities, it is useful to make a distinction between a persistent interictal memory deficit that may be present in patients with epilepsy on the one hand, and a transient amnestic period that might represent intermittent seizures or a postictal state on the other. It is the latter issue that is relevant to this chapter, with the focus being on whether seizures may cause transient intermittent amnesia. There are many ways to answer this question. At some level, all complex partial and generalized seizures are characterized by amnesia for the events that transpired during the seizure. But this conclusion is as unsurprising as it is uninteresting. It goes without saying, perhaps, that arousal and some perceptual ability are necessary for memory formation. Wakefulness, attention, and perception are just a few of the many cognitive functions that are disrupted as part of the diffuse impairment of cognitive function that accompanies widespread seizure activity. The more difficult, but also more interesting, question is whether isolated memory deficits may occur as the sole or predominant expression of seizure activity.

Before answering this question, it is helpful to clarify some of the concepts and terminology that are used in the evaluation of memory and the description of its deficits (Table 3). *Working memory*, also known as short-term memory or attention span, describes the active "online" holding and manipulation of information. It is under the control of frontal and prefrontal circuits. *Long-term* memory, on the other hand, refers to information that is stored "offline" for periods varying from minutes to years. The formation of stable long-term memories requires that information undergo encoding, consolidation, and storage and that there exist a mechanism to access or retrieve these memory engrams. This form of memory is mediated by mesial temporal and limbic connections. Although still debated, the available evidence from the seizure literature

Table 3
Memory—Glossary of Terminology

Registration	Process whereby information enters the nervous system via sensory input
Working memory	Online retention of information for a period of seconds to minutes
Encoding	Process whereby registered information is evaluated for relevance, subjected to associations and integrated with preexisting information
Consolidation	Process that leads to a deeper, more enduring sort of encoding
Storage	Representation of memory engrams in multimodal cortex
Retrieval	Recall of previously stored memory
Retrograde amnesia	Inability to retrieve information stored prior to the onset of the amnestic period
Anterograde amnesia	Inability to acquire new information for long-term storage and retrieval

suggests that the processes of encoding, consolidation, and retrieval are dissociable even though all three are mediated by medial temporal lobe and limbic structures. The ability to form stable long-term memories of a new experience is termed *anterograde* memory. *Retrograde* memory, on the other hand, refers to the ability to recall long-term memories that have already been established.

In general terms, the memory disturbance due to seizures may affect anterograde memory, retrograde memory, or a combination of the two. Anterograde amnesia may result from a disturbance of any number of cognitive processes involved in the formation of new stable long-term memories, including encoding, consolidation, storage, and retrieval. Temporary amnesia for previously acquired information (i.e., retrograde amnesia), however, is most likely to result from defective memory retrieval. The combination of antero- and retrograde amnesia has been termed *global* amnesia.

There are many reports in the literature of relatively isolated memory disturbances occurring as an ictal manifestation. A variety of different terms have been used to describe seizures that are characterized by a predominant memory disturbance. These include partial amnestic seizures, epileptic amnestic attacks, and transient epileptic amnesia. Irrespective of the term used to describe the event, the confidence with which one can accept that the memory disturbances described in these reports are in fact due to seizures, is variable. It is easiest to accept those reports that meet the following three criteria: (1) the patient was evaluated by a competent examiner during the event in question, (2) an EEG was obtained during the event in question and showed discharges consistent with an ongoing seizure (rather than simply the epileptiform discharges that might occur interictally), and (3) there was resolution of the clinical symptoms and electrographic changes upon administration of an anticonvulsant. There are a few reports that meet all these criteria. In addition, however, there are a fair number of reports that do not, but in which the evidence, although circumstantial, does support the contention that the transient memory disturbance is related to seizure activity. Frequently, these reports describe either

patients who have unequivocal seizures independently of the transient episodes of amnesia, or patients in whom the amnestic episode either follows a brief period of loss of contact, with or without automatisms, or is accompanied by clinical features very suggestive of a focal seizure such as olfactory hallucinations, feeling of déjà vu, or a rising epigastric sensation. Even in the absence of "ictal" EEG recordings in these latter cases, it seems reasonable to attribute the memory disturbance to either an ictal or a postictal manifestation. While at a purist level, it is important to distinguish ictal and postictal memory dysfunction, the distinction may have little practical value. If it is accepted that transient recurrent memory dysfunction may occur even as a postictal manifestation, this will be sufficient to consider epilepsy in the differential diagnosis of such episodes and to warrant further investigation and perhaps even a trial of anticonvulsant therapy.

3.2. Amnestic Status Epilepticus

Vuilleumier and colleagues provided the most unequivocal description of an isolated memory disturbance resulting from nonconvulsive status epilepticus *(12)*. They described the case of a 41-yr-old previously healthy woman who was found trying to enter her former house, where she had not lived for 3 yr. She was brought to the hospital, where she appeared calm and cooperative although a little perplexed. She answered questions appropriately and executed complex commands quickly and accurately. She did not engage in repetitive questioning. She was fully awake and alert, but was disoriented about time and profoundly amnestic. She knew her name, but not her address, phone number, or the contact details for a friend or relative. She was unable to give an account of her activities over the preceding few days (retrograde amnesia). Her digit span was 6, and from a 10-word list she recalled 4 words on the first two attempts and 6 words on the third attempt. She recalled only 1 word after a 3-min delay (apparent anterograde amnesia). The only other finding on examination was occasional rhythmic eye blinking. An EEG showed continuous generalized epileptic activity with rhythmic spikes at 3.5 to 4 Hz. Within 4 min of the administration of an intravenous bolus of 1 mg clonazepam, the EEG epileptic activity ceased and the patient said, "Now I can tell you . . . I recall everything . . . I can see all that happened . . ." She was able to provide an account of the events that had transpired over the preceding few hours. It appeared as though the episode had lasted about 10 h in total. It subsequently emerged that she had experienced a number of similar episodes since her teenage years and that these either occurred upon awakening in the morning or were preceded by an epigastric sensation. Treatment with carbamazepine was initiated and no recurrences were noted over the 6-mo follow-up period.

Lee and colleagues described the case of a young otherwise healthy woman who presented with acute onset of amnesia *(13)*. She had limited recollection of the events of the preceding 4 mo (retrograde amnesia) and examination showed normal working memory, but with failure to recall any of three words or three hidden objects after a 5-min delay (anterograde amnesia, involving both verbal and visual modalities). EEG with nasophargyngeal electrodes showed frequent

electrographic seizures arising from the left medial temporal lobe. Treatment with anticonvulsants led to the complete cessation of ictal discharges and was followed by complete recovery of her memory except for the events that had transpired during the course of her illness. The duration of her amnestic episode was 12 d. Though seizures were not ongoing, they occurred frequently during this period. It is not possible, therefore, to discern whether the memory dysfunction was an ictal or a postictal phenomenon. In the sense, however, in which she had recurrent electrographic seizures without complete recovery of memory function in between, it is reasonable to ascribe her prolonged amnestic period as being due to status epilepticus.

These case reports are of interest for a number of reasons. Most importantly, they establish unequivocally the possibility that an isolated memory disturbance may be the sole manifestation of nonconvulsive status epilepticus. Also of note is the variable nature of the memory disturbance. In the report by Vuilleumier and colleagues there was unequivocal retrograde amnesia as well as apparent anterograde amnesia during the seizure *(12)*. Following termination of the seizure, however, she was able to remember the events that had transpired during the seizure, indicating that anterograde memory was in fact preserved. The patient described by Lee and colleagues displayed a combination of anterograde and retrograde amnesia *(13)*.

3.3. Transient Epileptic Amnesia

There are many case reports and case series that describe patients with episodes of transient amnesia that are likely related to seizures. For the most part, these are reports of patients with recurrent, short-lived episodes of amnesia who had unequivocal seizures at other times, who had other symptoms suggestive of focal seizure activity preceding or during the amnestic attack, and who responded to treatment with anticonvulsants. For example, in the study by Zeman and colleagues (the largest case series published to date) *(14)*, the diagnosis of transient epileptic amnesia (TEA) required (1) a history of recurrent witnessed episodes of transient amnesia, (2) cognitive functions other than memory judged to be intact by a reliable witness, and (3) evidence for a diagnosis of epilepsy (based on epileptiform features on an interictal EEG, the cooccurrence of other seizure types, or a clear-cut response to anticonvulsants). The data from these reports are summarized in Table 4. As noted before, it is not possible to be certain whether the amnestic attacks represent ictal or postictal phenomena, but the distinction may not be important at least in terms of the therapeutic approach that is required. This table includes data from 32 patients with TEA. Anterograde amnesia was present in all but one patient, and most patients displayed a combination of antero- and retrograde amnesia. The attacks were recurrent in all but two patients and the frequency varied from 2 to 3 per week to 1 per year. The duration of attacks was of the order of minutes in most patients, lasted hours in a minority, and persisted for more than 24 h in only two patients. In the vast majority of patients, the frequency of TEA attacks was markedly reduced or attacks ceased completely following the initiation of anticonvulsant therapy.

Table 4
Ictal Amnesia

Reference	Amnesia	Repetitive questioning	Associated features	Recurrence	Duration	EEG	Response to AEDs
Lou *(23)*	A	Variable	Peculiar feeling in right arm and leg Mild aphasia	9 episodes	15–60 min	Slowing and sharp waves (I and I-i)	Unclear
Greene *(61)*	A + R	No	Slow speech and movement	None	4 h	Bitemporal spikes (I and I-i)	Not stated
Gilbert *(18)*	A + R	Yes	None	None	9 h	Bitemporal short sharp spikes (I-i)	Not stated
Dugan *(62)*	A	Yes	None	3 episodes	3 h	Bitemporal spikes (I, but not I-i)	Yes
Deisenhammer *(19)*	A + R	Yes	Headache; frightened and tearful	3 episodes	10 min	Mid-anterior temporal spikes (I and I-i)	Yes
Pritchard *(24)*							
Case 1	A	No	None	10 episodes	5–10 min	Mesiobasal temporal spikes (I-i)	Yes
Case 2	A > R	No	None	3 episodes	few hours	Mesiobasal temporal spikes (I-i)	Yes
Gallassi *(20–22)*							
Case 1	A + R	Yes	Loss of contact and automatisms and occasional epigastric aura prior to amnestic episodes	25 episodes	10–60 min	Temporal excess slowing (I-i)	Yes

Case 2	A + R	Yes	Loss of contact and automatisms	2–3 per week	10–60 min	Paroxysmal right temporal activity (I-i)	Yes
Case 3	A + R	Yes	Loss of contact and automatisms	1 per month	10–60 min	Temporal slowing (I-i)	Yes
Case 5	A + R	Yes	Loss of contact; automatisms	1–2 per month	10–60 min	R > L temporal slowing (I-i)	Yes
Case 7	A + R	Yes	Loss of contact	1 per month	10–60 min	Paroxysmal R temporal activity (I-i)	Yes
Case 8	A + R	Yes	Loss of contact	1 per year	10–60 min	R temporal slowing (I-i)	Yes
Case 9	A + R	Yes	Loss of contact; automatisms	5–7 per year	10–60 min	L > R temporal slowing (I-i)	Yes
Case 12	A + R	Yes	Loss of contact and dizziness	2–3 per year	10–60 min	Bilateral temporal slowing (I-i)	Yes
Case 13	A + R	Yes	Loss of contact; automatisms	2–3 per week	10–60 min	Paroxysmal L temporal activity (I-i)	Yes
Stracciari *(63)*	A > R	Yes	Loss of contact; automatisms	8-10 episodes	minutes–hours	Temporal slowing; small sharp spikes (I-i)	Yes
Meador *(64)*	A or R	No	Micropsia briefly; loss of contact	2 episodes	10–15 min	Bilateral epileptiform discharges (I-i)	Yes
Kopelman *(25)*	A	Yes	Fist clenching on two occasions	9 episodes	30–60 min	Temporal sharp & slow wave complexes	Yes
Kapur *(65)*							
Case 1	A + R	Yes	Lip smacking and gulping	35 episodes	minutes–hours	L temporal slowing (I-i)	Yes

(continued)

Table 4 ***(Continued)***

Reference	Amnesia	Repetitive questioning	Associated features	Recurrence	Duration	EEG	Response to AEDs
Case 2	partial A	?	Some warning of the attack	2 episodes	30–60 min	L temporal slowing (I-i)	Yes
Case 3	A + R	No	Automatisms	1–2 per month	1–2 d	Bursts spike & slow waves (I-i)	Yes
Case 4	R	No	Preceding period of "confusion"	2 episodes	minutes	Not reported	Yes
Zeman *(14)*							
Cases 1–10	A + R	Yes	Olfactory hallucinations; déjà vu; vertigo	2–30 (mean 9)	<1 h (n = 6) h–d (n = 2)	Epileptiform activity (I-i) in 4 patients	Yes

A, anterograde; R, retrograde; I, ictal EEG; I-i, inter-ictal EEG; R, right; L, left.

3.4. Transient Global Amnesia

Much of the literature about seizures and memory has been presented in the context of similarities to the syndrome of transient global amnesia (TGA). TGA is a syndrome characterized by the acute onset of a global (anterograde and retrograde) memory deficit that persists for a number of hours and usually resolves gradually within about a 24-h period. The syndrome is most common in men over the age of 55, and the affected individual is usually able to continue with complex activities but asks the same questions repetitively despite their being answered appropriately. The etiology of TGA is unknown, with suggested possibilities including focal cerebral ischemia, migraine variant, or seizure activity. Hodges and Warlow have argued that much of the confusion surrounding the etiology of TGA results from lack of generally agreed-upon diagnostic criteria *(15)*. As explained in the discussion that follows, there may be a number of features of the attack that facilitate a relatively easy distinction between TEA and TGA.

TEA and TGA bear a number of phenotypic resemblances. Each may be characterized by the occurrence of short-lived periods of global amnesia. In both instances, patients are able to continue with otherwise complex activities due in large part to the amnesia occurring as an isolated cognitive deficit. One of the classical findings in patients with TGA is the presence of repetitive questioning despite receiving adequate answers to the questions. As evident from Table 4, this feature has also been documented to be present in the majority of patients with TEA. How then can the two be differentiated? Some important clues emerged from the case-control study of Hodges and Warlow *(15)*. They examined 153 patients with acute transient memory loss in an effort to better classify patients with this clinical syndrome. One aim of the study was to determine whether patients with differing prognoses could be identified on the basis of their clinical features at presentation. With respect to the distinction between those who went on to develop epilepsy and those who did not, two important conclusions emerged. The first was that there existed a strong association between the number of attacks at presentation and the subsequent development of epilepsy. The second was that the duration of the episode had high predictive value, with the shorter duration of attacks (i.e., less than 1 h) predicting subsequent development of epilepsy. The positive predictive value for epilepsy when both features were present (i.e., a history of a preceding attack and duration of the present attack being less than 1 h) was 100% and the negative predictive value when both were absent was 96.4%. The crucial differences, therefore, between TEA and TGA are the relatively short duration and recurrence of attacks in TEA as well as the presence of other features suggestive of epilepsy (hallucinations, brief loss of contact, automatisms, etc.) and the responsiveness to anticonvulsant therapy.

3.5. Postictal Amnesia

Tassinari and colleagues reported the case of a 60-yr-old man with a 3-yr history of recurrent "memory spells," each lasting 10 to 15 min *(16)*. Video-EEG monitoring captured two seizures. Each was characterized by the sudden onset of olfactory

hallucinations, a rising epigastric sensation, repetitive chewing movements, and brief loss of contact. The seizures lasted almost 1 min and were characterized electrographically by bilateral 4–5 Hz paroxysmal activity. Each seizure was followed by an amnestic state during which the patient had no recollection for events of the previous few days (retrograde amnesia) and was unable to retain any new information (anterograde amnesia). He repeatedly asked the same questions despite being provided with adequate answers by the examiner. The EEG was normal during the amnestic period. He was treated with carbamazepine and had no further amnestic attacks over the following 16 mo.

This case report is important primarily because of the availability of video-EEG monitoring during the amnestic attacks as well as the documentation of a careful neurologic examination during this time. It is possible, therefore, to clearly delineate these amnestic episodes as a postictal phenomenon. Also of note is that each individual amnestic episode experienced by this patient was clinically indistinguishable from the syndrome of TGA. The differences, of course, lie in the recurrent nature of the attacks in this patient as well as their response to anticonvulsant medication.

3.6. Clinical Manifestations of Ictal Amnesia: a Summary

It should be apparent from the foregoing discussion that the amnestic phenotype of transient epileptic amnesia is highly variable. Most reports describe a combination of anterograde and retrograde amnesia *(14,17–22)*, and it is these patients who bear the strongest phenotypic resemblance to those with TGA. In addition, there are also reports of patients with isolated retrograde amnesia *(12)* and pure anterograde amnesia *(23–25)*. Most recently, there has emerged a report of a patient with selective impairment of consolidation *(26)*. The author described the case of a middle-aged woman with recurrent amnestic episodes. On one occasion she had been horseback riding and found herself walking to her house, not remembering the ride or putting the horse in the stable. Neurologic examination was described as normal. She was evaluated during one such spell. The examiner noted that he showed her a $20 bill before leaving the room, but found that she remembered neither him nor the $20 bill when he returned the next day. She was monitored with video-EEG, at which time she had multiple ictal events during which she reported feeling cold and having gooseflesh. Memory testing during the episodes was normal. Surface EEG with nasopharyngeal electrodes showed bilateral temporal ictal discharges. Subsequent monitoring with depth electrodes confirmed the presence of bilateral hippocampal seizures. She was subsequently amnestic for these spells. This, therefore, is an example of a patient with episodes characterized by preservation of previously acquired information, but loss of information acquired during the time of the seizure; and the occurrence of the seizure being apparent to the patient or the observer only sometime after the seizure had ended. The memory deficit in this case is perhaps best described as a defect of post-encoding consolidation.

3.7. Conclusion

It should be clear, therefore, that the ictal etiology of transient memory disturbances cannot be discerned on the basis of the amnestic phenotype. The feature most useful in recognizing a seizure as the cause of a transient memory deficit is the brevity of the attack. A history of similar episodes in the past is also extremely helpful. Finally, a careful history and examination may disclose subtle ictal manifestations such as a history of déjà vu, olfactory hallucinations, a rising epigastric sensation, automatisms, and/or a brief period of loss of contact. Under appropriate circumstances, an empiric trial of anticonvulsant therapy may be appropriate, and a beneficial response validates the suspicion that the events were ictal in origin.

4. ICTAL PSYCHOSIS

4.1. Introduction

The relationship between epilepsy and psychosis is a complex one. Conceptually, it is helpful to recognize three distinct entities—*ictal*, *postictal,* and *inter-ictal* psychosis. The last term refers to the psychosis that may occur in patients with epilepsy in whom the symptoms are not temporally related to seizures. *Inter-ictal* psychosis has been the subject of many studies, with most investigators describing symptoms reminiscent of schizophrenia *(27–30)*. The basis for the psychosis is unclear, but it may be that the underlying pathology of the temporal lobe is responsible for generating both the seizures and the psychosis. Distinct from interictal psychosis are ictal psychosis, in which the psychotic symptoms are the direct manifestation of seizures, and postictal psychosis, in which the psychotic symptoms follow seizures. Finally, there is a syndrome referred to in the literature as "alternating psychosis" or "forced normalization," in which the onset of psychosis follows the suppression of electrographic seizure activity.

Traditionally, the gold standard used for determining whether particular symptoms are due to underlying seizure activity is the documentation that the symptoms occur concurrently with ictal electrographic activity. However, in considering whether episodic psychotic symptoms are ictal in origin, it is important to recall that the surface EEG is of limited utility in demonstrating the electrographic activity of mesial temporal lobe and other deeper or frontal structures. The over-reliance on EEG evidence of ictal activity, therefore, for the diagnosis of ictal or postictal psychosis will likely lead to an underestimation of the prevalence of this disorder. It may be necessary, therefore, to rely more heavily on the sort of circumstantial evidence referred to previously in this chapter. This evidence includes a history of other events clearly recognizable as seizures, the presence of associated symptoms during the psychotic period that are more readily identified as being ictal in origin (e.g., staring spells or automatisms), or a favorable response to anticonvulsant therapy.

By way of introduction, it is also necessary to say something about the nature of psychosis. The term *psychosis* is a difficult one, in part because it is taken to mean different things under different circumstances *(31)*. A minimalist view restricts psychosis to the presence of delusions or prominent hallucinations, with

the hallucinations occurring in the absence of insight into their pathological nature. A much broader definition would include other positive symptoms of schizophrenia such as disorganized speech and grossly disorganized or catatonic behavior. In essence, therefore, psychosis is defined by the presence of certain symptoms and although there is disagreement about which symptoms warrant usage of the term, it is the presence of delusions or hallucinations that is most basic. As defined by the *Diagnostic and Statistical Manual of Mental Disorders*, (DSM-IV), delusions are "erroneous beliefs that usually involve a misinterpretation of perceptions or experiences." Delusions may assume a variety of themes, including persecutory, referential, somatic, religious, or grandiose. Thought insertion, withdrawal, and broadcasting are examples of delusions. Hallucinations are more self-explanatory and may occur in any sensory modality—auditory, visual, olfactory, gustatory, or tactile.

4.2. Ictal Psychosis

The term *ictal psychosis* describes the occurrence of psychotic symptoms in association with epileptiform activity on EEG; it is an example of nonconvulsive seizure activity. This remains a somewhat controversial entity as there are only a limited number of descriptions of this disorder in the literature *(32,33)*. In the largest published series, Tucker and colleagues described 20 patients who were admitted to a psychiatric service because of behavioral disturbances and were subsequently found to have temporal lobe epilepsy *(34)*. The clinical details of these and other patients are summarized in Table 5. Only six patients had a known history of epilepsy. All patients also reported "spells" characterized by losing track of time, staring, feeling dazed, or being in a dreamlike state. The majority (70%) of patients described intense affective symptoms, either panic-like attacks or depressive mood swings, with the characteristic features being their episodic nature, abrupt onset, and sudden remission. Other common symptoms included paranoid ideation (30%), Schneiderian first-rank symptoms (25%), and hallucinations (auditory in 50%, visual in 40%, olfactory in 30% and tactile in 10%). Important features that facilitated the diagnosis of epilepsy included the episodic nature of the symptoms and the consistency of the symptoms in each patient over time.

While this is perhaps the best published series of cases with putative ictal psychosis, it is relevant to note that an ictal EEG was obtained in one patient only. In the remaining patients, most interictal EEGs were abnormal, but they showed nonspecific findings that do not clearly represent potentially epileptogenic activity. On the other hand, the episodic nature of the symptoms with many of the associated clinical features typical of temporal lobe complex partial seizures, as well as the response (partial or complete) to anticonvulsant therapy, provide strong circumstantial evidence that these patients did have underlying epilepsy.

4.3. Postictal Psychosis

Postictal psychosis has been the subject of greater study and is probably not uncommon *(35)*. There are, however, relatively few detailed reports of its clinical

Table 5
Ictal Psychosis

Reference	Clinical symptoms	EEG	Response to treatment
Takeda *(32)*	Mood lability; A hallucinations; restless, anxious, fearful; estranged from the outside world	L amyg rhyth spikes	Complete response
Tucker *(34)*			
Case 1	V and A hallucinations; psychotic thoughts; mood lability; "spells" of being out touch with the environment; episodic suicidal ideation	R sided PLEDS	Partial response
Case 2	V, A and O hallucinations; déjà vu; depersonalization; mood lability; command hallucinations; staring spells; episodic suicidal ideation	Paroxysmal 4–5 Hz slowing on R+L	Partial response
Case 3	"Flashbacks" with panic; mood lability, déjà vu; depersonalization; forced thoughts; left body autonomic symptoms	Excess slowing	Complete response
Case 4	Episodic somatic delusions; staring spells	Diffuse S&SW	Complete response
Case 5	Episodic paranoid ideation and trance-like behavior	R temporal spikes	Partial response
Case 6	Spells of losing track of time and staring; command A and V hallucinations; mood lability	Normal	Partial response
Case 7	Spells of lip smacking; episodic nihilistic ideation, panic attacks and psychotic behavior	L temporal spikes	No response
Case 8	Episodic feelings of possession, paranoia and first-rank symptoms; A, O, and T hallucinations	Paroxysmal slowing	Complete response
Case 9	Staring spells; flashbacks; forced thoughts; V, A and O hallucinations; depersonalization	Normal (I)	Markedly improved
Case 10	Episodic paranoia; mood lability; staring spells with bizarre behavior; hallucinations	Bilateral S&SW	Complete response
Case 11	A hallucinations; mood lability; trances; depersonalization; self-mutilation; racing thoughts	Rhythmic slowing R+L	Partial response
Case 12	Auditory illusions; automatisms	Non-specific	Complete response
Case 13	Polyopia; panic attacks; suicidal ideation; forced thoughts; spells with automatisms	R+L spikes	Complete response

(continued)

Table 5 ***(Continued)***

Reference	Clinical symptoms	EEG	Response to treatment
Case 14	Staring spells; episodic dyscontrol; paranoid and suicidal ideation; A and V hallucinations	Non-specific	Partial response
Case 15	Suicidal ideation; episodic violence; staring spells with automatisms	Rapid S&SW	Complete response
Case 16	Episodic fear with racing and intrusive thoughts; spells; O, V, and command A hallucinations; suicidal and paranoid ideation; episodic blocking and loosening of associations; mood lability	Paroxysmal changes	Partial response
Case 17	V, O, T, and A command hallucinations; mood lability; episodic suicidality; clang associations	Bursts of S&SW	Partial response
Case 18	Episodic dyscontrol; staring spells; episodic anxiety and suicidality; déjà vu; depersonalization	Intermittent S&SW	Complete response
Case 19	Episodic loss of contact, self-mutilation suicidality; automatic and bizarre behavior	Non-specific	No response
Case 20	Episodic dyscontrol & suicidality; A, V, and O hallucinations; mood lability; déjà vu	L S&SW	Partial response
Tisher *(33)*			
Case 1	Episodic command auditory hallucinations, usually but not always ego-dystonic	Paroxysmal activity	Not stated

EEGs are inter-ictal unless otherwise designated as ictal (I); V, visual; A, auditory; O, olfactory; T, tactile hallucinations; R, right; L, left; PLEDs, periodic lateralized epileptiform discharges; S&SW, spike and slow wave; amyg, amygdala; rhyth, rhythmic.

Table 6
Postictal Psychosis

Clinical context	• Usually occurs in a patient with known history of epilepsy • Typically follows a prolonged seizure or a flurry of seizures • There is usually an intervening lucid interval between the end of the seizure and the onset of the psychosis (variable duration)
Type of psychosis	• Delusional • Affective-like • Schizophrenia-like
Delusions	• Often of the paranoid variety • Usually poorly systematized, but may be well-systematized
Hallucinations	• Visual > auditory > tactile or olfactory • May be multimodal in a minority of cases

symptomatology *(36–39)*. Psychosis may develop following either primary generalized *(37,38)* or complex partial seizures *(36)*. In the majority of patients there is a clear history of either a prolonged seizure or an increased seizure frequency prior to the onset of psychosis *(40)*. In some instances it may be precipitated by abrupt withdrawal or a change in anticonvulsant therapy *(39)*. Full recovery from the seizures and postictal confusion are observed in most patients, with psychosis developing after a lucid interval lasting anywhere from a few hours *(38–40)* to 1 mo *(36)*. Paranoid delusions (that are typically, but not always, poorly systematized) are common *(36–39)*, as are affective disorders *(36,37)*. Hallucinations are most frequently visual, less often auditory, and rarely tactile or olfactory *(36,37)*. Multimodal hallucinations occur in a significant minority of patients. In the end, postictal psychosis is a heterogeneous disorder with features that may resemble a paranoid delusional syndrome, a schizophrenia-like illness, or an affective disorder. The clinical features are summarized in Table 6.

4.4. Conclusion

That psychotic symptoms may occur in a close temporal relationship to seizures seems undeniable. For reasons that in part relate to the difficulties of studying the electrographic correlates of episodic psychosis, it may often be difficult to clearly distinguish ictal from postictal psychosis. Nevertheless, the distinction from primary psychosis (e.g., schizophrenia) should not be too difficult. Those with ictal or postictal psychosis (or both) usually have a history of prior seizures, and the psychotic symptoms occur episodically, often with abrupt onset and relatively short duration. Nevertheless, when confronted by a patient in the midst of a first psychotic episode, particularly when relatively little is known about an earlier history, it is useful to consider nonconvulsive status epilepticus in the differential diagnosis.

5. DISCUSSION

Aphasia, amnesia, and psychosis are not the only cognitive manifestations of seizures, but they are important, at least in part because of their place in the differential diagnosis of other disorders that may produce the same clinical features. Transient

aphasia is usually considered a manifestation of cerebral ischemia, and the recognition that an isolated aphasia may also result from seizure activity has important implications for the investigation and treatment of patients who present in this way. Transient amnesia may similarly be due to ischemia, but it also raises the differential of the more benign syndrome of TGA. The clinical presentation of transient epileptic amnesia may resemble that of TGA, and the two disorders may be distinguished by the presence of a prior history of similar attacks in the past, as well as by the duration of the individual episodes. The distinction between the two has important implications for prognosis and treatment. Finally, patients with psychosis usually (but not exclusively) present to psychiatrists rather than to neurologists. Recognizing that psychosis in a particular individual is epileptic in origin rather than due to schizophrenia or some other primary psychiatric condition also has important therapeutic and prognostic implications.

In trying to discern the epileptic etiology of these and other cognitive disturbances, it is necessary to investigate carefully for the presence of subtle ictal manifestations such as a history of déjà vu, olfactory hallucinations, a rising epigastric sensation, automatisms, or a brief period of loss of contact. These features may have been present at other times or may accompany the transient episodes of aphasia, amnesia, or psychosis. Similarly, a history of prior attacks, especially with stereotyped symptoms, is very suggestive of an epileptic etiology. The suspicion that seizures underlie the clinical presentation should prompt investigation with an EEG, but it is important to remember the limitations of surface EEG recordings for ictal and interictal discharges arising from mesial temporal and frontal lobe structures. Under appropriate circumstances, an empiric trial of anticonvulsant therapy may be appropriate.

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12

Nonconvulsive Status Epilepticus

Morbidity and Consequences

Frank W. Drislane

Nonconvulsive status epilepticus (NCSE) is protean in its clinical manifestations and often difficult to recognize. It is clearly underdiagnosed. It has a tremendous variety of precipitants or causes. The complexity in categorization or classification makes it difficult to determine its morbidity or consequences. NCSE comprises many different illnesses, such that diagnosis and management are different for the many types, and the prognosis varies accordingly. Neurologists generally agree that episodes of NCSE should be avoided or treated, but the consequences and long-term risks are varied, difficult to ascertain, and controversial.

There are many types of outcome to consider. Mortality from NCSE itself (as opposed to that from the underlying lesion or precipitating illness) is rare. "Brain damage" or neuronal injury is extremely difficult to be sure of. Consequences can be studied from the point of view of experimental animal studies, human pathologic studies, and, primarily, clinical reports. In addition to mortality and adverse structural consequences, morbidity can include physical injury during NCSE, treatment complications, recurrences of status epilepticus, longer-term cognitive deficits, and the likelihood of NCSE leading to or exacerbating epilepsy. Recurrence is probably the most common complication. Most other morbidity is assessed by clinical neurologic evaluation, particularly for memory, cognitive, and other neurologic deficits.

1. EXPERIMENTAL STUDIES IN ANIMALS

Many superb experimental models of generalized convulsive status epilepticus (GCSE) have aided immensely our understanding of the physiology, pathophysiologic mechanisms, and consequences of GCSE. Models of NCSE are far more difficult to design and to learn from.

The experiments of Meldrum and colleagues in the 1970s established that episodes of convulsive SE lasting up to several hours produce substantial neuronal damage in the neocortex, cerebellar Purkinje and basket cells, and hippocampal cells in baboons *(1–3)*. The SE was initiated by systemically administered bicuculline and included major electrolyte and acid–base disturbances, hyperpyrexia, and cardiac

From: *Current Clinical Neurology: Status Epilepticus: A Clinical Perspective*
Edited by: F. W. Drislane © Humana Press Inc., Totowa, NJ

arrhythmias *(1)*. The hours of SE included rapid epileptiform discharges punctuated by flat periods on the electroencephalogram (EEG).

Much of the ensuing cellular damage correlated with hyperpyrexia, hypotension, hypoxia, acidosis, and hypoglycemia. Controlling for these factors by paralysis and artificial ventilation reduced the damage in the neocortex, thalamus, and hippocampus, showing that systemic factors contributed to some of the injury *(3)*. Maintenance of homeostasis, however, provided incomplete protection in the neocortex and hippocampus. Hippocampal neuronal loss was still substantial, suggesting strongly that the electrical activity of SE damages hippocampal neurons independent of systemic and metabolic factors. These experiments provided a model primarily for GCSE. Importantly, they indicated that the brain activity associated with GCSE (even without convulsions) was damaging by itself. The question of damage from NCSE was not addressed directly.

Lothman and colleagues demonstrated that excitotoxins, particularly kainic acid (whether applied systemically or locally in the hippocampus) affected limbic structures preferentially. Kainic acid produced seizures that were primarily nonconvulsive, providing more of a model of NCSE *(4,5)*. To overcome concern that the neuronal injury following such seizures was due to a toxic effect of kainic acid directly on the neurons, they also used electrodes implanted in the rat hippocampus *(6,7)*. Rapid repetitive electrical stimulation for 30 to 90 min produced seizures and eventually self-sustaining SE persisting for 12 to 24 h after the stimulation ceased. Stimulation included 10-s periods of 50 Hz, 1-ms pulses alternating with 3 s for EEG recording, with the entire episode lasting 90 min. It produced electrographic seizures with very rapid epileptiform discharges, often more than 10 Hz. Later seizures were nonconvulsive and described as "limbic," with prominent hippocampal discharges rather than generalized convulsions. This model also led to neuronal loss in the hippocampal CA-1 region. Interestingly, however, rats with briefer or less-frequent seizures did not sustain the same injury *(8)*. Some of the limbic changes were reversible, resolving after weeks *(7)*. The experiments thus raised the possibility that damage from NCSE might be less substantial or less permanent than that from GCSE.

There is concern that the chemical and electrical methods of inducing SE may damage neurologic tissue themselves, independent of the electrical discharges of seizures or SE. To obviate these concerns, Sloviter showed that indirect electrical stimulation via the perforant pathway (the primary afferent excitatory pathway to the hippocampus) could lead to damage in rat hippocampal neurons *(9)*. This avoided direct injection of potentially toxic chemicals or penetrating electrodes. Typical stimulations, however, were vigorous: 1-ms pulses of 20 V at a 2 Hz frequency maintained for 24 h, with additional 10-s runs of 20-Hz activity once a minute.

The typical stimulations used to provoke seizures and SE in these models have been intense. The intensity of the resulting epileptiform discharges appears to correlate with the likelihood of subsequent neuronal damage. Localized prepiriform bicuculline injection produced both heat shock protein (HSP; a sign of neurologic damage) and neuronal death in the thalamus, amygdala, and piriform cortex in

rats *(10)*. Of note, HSP was produced by high-frequency epileptiform discharges only. The same group used flurothyl to induce seizures in paralyzed and ventilated rats and found that HSP production was associated strongly with "high-frequency" (approx 10 Hz) epileptiform discharges and especially those lasting longer than 20 min. There was no such damage with high-voltage spike and sharp wave discharges with a frequency of less than 1 Hz *(11)*. They concluded that neuronal damage was related directly to the duration and intensity of electrographic seizure activity.

These many experiments helped elucidate the neuroanatomy, pathophysiology, and mechanisms of neuronal damage from neurotoxins, excitotoxins, and electrical stimulation in several different models of SE. In the different types of human SE, however, the electrical activity varies considerably, and the epileptiform discharges recorded in most of the models was far more sustained, rapid, and intense than those found typically in human NCSE. While the animal behavioral changes that result from such stimulation are consistent with complex partial or other types of NCSE, the original electrical disturbance is often more suggestive of the electrical activity in GCSE. Rapid epileptiform discharges greater than 3 Hz are common in generalized convulsions in humans *(12)*. Even in experimental studies of SE without convulsions (those using paralysis and physiologic controls) and presumably without the concomitant systemic derangements, the epileptic electrical activity is intense—more so than in human NCSE. Clinical NCSE may be sustained for hours or days, but it seldom includes high-frequency discharges characteristic of generalized convulsions in humans or in the experimental models described so far.

Hosford points out the remarkably consistent neuropathologic sequelae of seizures in most of these models *(13)*. The convergence of many models suggests that different stimuli leading to NCSE may all, when intense enough, lead to long-term neuronal loss and presumably damage that has a clinical effect. It also suggests that the damage results from the neuronal electrical activity rather than from the inducing agents. All the models may involve excessive glutamate receptor activity *(14)*, but other factors may make a large difference in the amount of neural injury.

As stated by Hosford, "valid animal models of human NCSE should share behavioral and electrographic features of human NCSE *(13)*." At best, this should involve the same neural structures, show the same response to antiepileptic drugs, and produce similar neuropathologic consequences. The self-sustained limbic SE model produced by prolonged hippocampal stimulation *(6)* did not respond to phenytoin as well as human complex partial NCSE often does *(8)*, indicating some limitation of this model's applicability to human NCSE.

In terms of more specific clinical types of NCSE, models of absence NCSE include genetically abnormal "tottering" and other mouse models with well-identified genetic abnormalities. These models demonstrate no pathologic damage in neurons despite frequent seizures *(13)*. Even administration of the toxin pentylenetetrazol in models for absence seizures (used in antiepileptic drug testing) does not produce neuropathologic changes *(13)*.

In summary, the many experimental animal models of NCSE have clarified physiologic changes in NCSE and particularly in the neuronal structures involved in its manifestations. Many of the models, however, are easier to apply to GCSE or to the consequences of NCSE in subjects with earlier lesions, particularly in limbic areas *(15)*. Also, many of the models establish a clear correlation between the intensity and duration of the electrical seizure activity on the one hand and the extent of neuronal damage on the other. The physiologic intensity of most nonconvulsive seizures or NCSE in humans typically falls below that seen in GCSE in the animal models that produce long-term neuronal damage. Less intense seizure activity may lead to minimal or no neuronal damage *(11)*. The variety of human NCSE is great, and the experimental models may apply better to some of these syndromes than to others. It is not clear when the threshold of intense seizure activity causing damage is crossed in the different human syndromes, so findings from human pathologic and clinical studies must be examined.

2. HUMAN PATHOLOGIC STUDIES

Pathologic studies of the effects of status epilepticus in humans are few, in part because fatal SE is often associated with acute, severe brain-injuring illnesses such as ischemic strokes, hemorrhages, tumors, severe trauma, and encephalitis, all of which can cause substantial damage independently. DeGiorgio and colleagues performed a case-control study of hippocampal cell densities in patients who died after episodes of GCSE, in comparison to patients with epilepsy but no episodes of SE and to normal controls *(16)*. Each group had five patients, matched as well as possible for cause of seizures in the epilepsy group and for age in controls. Episodes of GCSE typically lasted a few hours. SE patients had significantly decreased neuronal densities in the hippocampal presubiculum compared to normal controls and somewhat less than in epilepsy controls. This suggested that the episodes of GCSE were responsible for the additional damage.

Three patients were reported with focal motor SE (not nonconvulsive, but without systemic metabolic derangements or lesions known to cause longer-term epilepsy) *(17)*. The SE lasted 9 to 72 h and was accompanied by unilateral or independent bilateral discharges. These patients incurred neuronal loss and gliosis in the hippocampus, amygdala, and dorsomedial thalamus, as well as cerebellum, piriform, and entorhinal cortices. One patient had leptomeningeal carcinomatosis and a seizure 2 mo before the focal SE, but there was reason to believe that the meningeal disease did not affect the brain parenchyma significantly. In two patients the cause of focal SE was not clear.

Much more scarce are pathologic studies of patients with NCSE; those with "completely nonconvulsive" SE are vanishingly rare. Such episodes are seldom fatal unless they occur in association with GCSE or other acute, severe neurologic illnesses, in which case it is difficult to identify a single offending agent. There is brief mention of three patients without prior epilepsy who had NCSE lasting from 2 h to 3 d and who died within 4 wk; all had neuronal loss in the hippocampus *(18)*. For the most part, however, pathologic studies of patients with pure forms of NCSE are unavailable.

3. HUMAN CLINICAL LABORATORY STUDIES

There are other possible markers of neuronal damage in humans short of histopathology. Serum neuron-specific enolase (NSE) is elevated in acute brain injury, including strokes and other acute lesions. DeGiorgio and colleagues found it elevated in several forms of SE *(19)*. NSE was higher in patients with CPSE, but also elevated in those with absence SE. Absence status epilepticus (ASE), however, almost always has an excellent clinical outcome without any neurologic deficit, so the NSE elevation is difficult to interpret. Another study found NSE levels within a normal range in patients with ASE *(20)*. Two other patients (one with generalized and one with regional EEG sharp waves) had elevated NSE in episodes of NCSE but no reported long-term clinical deficits *(21)*. In some cases of SE, elevated NSE may represent neuronal injury, but some injury is reversible. The clinical significance is not definite yet.

Several studies have found functional magnetic resonance imaging (MRI) or blood flow changes in cases of SE—mostly convulsive. Diffusion weighted imaging (DWI) and T2 signals were abnormal in areas thought to be involved in the SE. They resolved on retesting in at least one report *(22)*. DWI changes were also prominent in another patient with NCSE *(23)*. The abnormalities included widespread cortical hyperintensity with decreased apparent diffusion coefficient on DWI. Some of the DWI changes resolved, but local atrophy appeared to ensue. These findings are worrisome for cortical injury even in NCSE, but the clinical correlate often appears fleeting.

4. CLINICAL STUDIES

Most clinical studies indicate that the neurologic morbidity or clinical consequences of NCSE are minimal, at least when divorced from the morbidity of any underlying illness or precipitant that leads to NCSE. Nevertheless, this is a complicated field.

Some uncertainty about the morbidity and outcome in NCSE is due to the relative youth of this field of clinical inquiry. While isolated cases of NCSE were probably described centuries ago (*see* Chapter 1) it was relatively unknown to early epileptologists. Only after the development of the EEG and demonstration of absence seizures in the 1940s did NCSE begin to attract attention *(24)*. Schwab described a case of prolonged petit mal status in 1953 *(25)*, Niedermeyer and Khalifeh described "spike wave stupor" in 1965 *(26)*, and it was only in the 1970s that several larger case series were published, such as that of Andermann and Robb on ASE *(27)*. Most studies on NCSE date from the past two decades.

A greater problem in elucidating the morbidity and prognosis of NCSE has been lack of agreement on diagnostic criteria and classification. NCSE has protean presentations (*see* Chapter 10) and may be very difficult to diagnose. Some have drawn the false impression that NCSE is rare.

Studies are, in fact, not limited by a paucity of cases. About 30 yr ago, Celesia stated that NCSE constituted nearly a quarter of SE in a moderate-sized series *(28)*.

Subsequently, Shorvon estimated from the prevalence of different types of epilepsy, and the incidence of episodes of SE in each, that there were approx 3.5 cases of complex partial SE and 15 cases of other NCSE per 100,000 population per year *(29)*. Interestingly, DeLorenzo and colleagues calculated, from ascertainment of actual cases, an incidence of about 60 cases of SE/100,000/yr in the United States *(30)*. Together with Shorvon's figures, this would corroborate Celesia's estimate of one quarter of all SE. Still, the diagnosis is often missed, and any ascertainment must be an underestimate. Tomson and colleagues found 1.5 cases of NCSE/100,000/yr in Sweden, about one tenth the estimated incidence *(31)*. NCSE is clearly underdiagnosed; this and the difference of opinions on appropriate definitions of NCSE surely reinforce one another.

Definitions of NCSE continue to be controversial (*see* Chapters 2 and 10). At a minimum, all patients have clinical neurologic deficits, particularly alterations in alertness and responsiveness. The associated EEG findings and a rapid response to antiepileptic drugs (AEDs), particularly benzodiazepines, are variable and are more controversial parts of diagnostic criteria.

Different studies on the outcome of NCSE have used different diagnostic criteria, and patient populations in these studies are seldom "pure." Some studies describe patients with relatively classic ASE with 3/s generalized spike and slow-wave discharges. Others include patients who are unlikely to have simple absence seizures and may have rhythmic generalized discharges more suggestive of secondary generalized seizures—still appearing clinically like patients with absence seizures. Some papers restrict themselves to clinical features supporting a diagnosis of complex partial SE. Others include both these conditions under the rubric of nonconvulsive status.

There are also other types of NCSE, including those relatively rare patients with focal nonconvulsive SE (other than complex partial SE) such as those with purely sensory symptoms or patients with aphasic SE. There are several childhood syndromes, such as atypical absence status, electrical status epilepticus of sleep (ESES), and so-called "epileptic encephalopathies"—which are primarily covered in the chapters on pediatric and neonatal forms of SE.

Finally, there are many patients with nonconvulsive forms of SE caused or precipitated by acute medical and neurologic illnesses such as strokes, infections, or metabolic derangements, in which patients (often comatose) have good EEG evidence of ongoing SE but may or may not respond well to AEDs. As with individual seizures (whether part of chronic epilepsy or "acute symptomatic" seizures), the etiology is almost always the chief determinant of morbidity and outcome. These patients should be considered separately from those in whom epilepsy is the sole or dominant illness. Almost always, patients with individual seizures or SE (including nonconvulsive forms) caused by acute medical or neurologic illness fare far worse than those with seizures, epilepsy, or status epilepticus alone.

4.1. Absence Status Epilepticus

ASE in a relatively classic or pure form includes patients with generalized 3-Hz epileptiform discharges on EEG who have no features of a focal epilepsy. Pure cases

represent very prolonged absence seizures and typically occur in patients with earlier primary generalized epilepsy syndromes. Typical clinical manifestations include confusion, with occasional blinking or myoclonus. Episodes may last up to days. Medication withdrawal or other precipitants may prompt an episode. Early series of such patients were described by Andermann and Robb *(27)* and by Niedermeyer and Khalifeh *(26)*. More recently, episodes have been reported in older patients with no prior epilepsy, "*de novo* SE," often associated with withdrawal of benzodiazepines, at times used for anxiety or sleep *(32)*.

Andermann and Robb described 38 patients. Diagnosis was not at all obvious, and many patients may have been missed. Episodes lasted 30 min to 2 d. During the episodes, responsiveness fluctuated, and patients were often unable to perform continuing tasks. An unspecified number had recurrences. One patient appeared to have episodes every few weeks over 25 yr. Other than recurrence, sequelae were not reported, and there was no mention of any long-term dysfunction. Niedermeyer and Khalifeh detailed petit mal status or "spike wave stupor" in six patients. All had had earlier generalized convulsions, and at least two had had earlier absence seizures. No long-term sequelae were noted, but follow-up data were not supplied.

Prognosis varies somewhat if ASE is further subclassified *(33)*. One report detailed 11 older patients with *de novo* ASE *(32)*. Several had myoclonic jerking, automatisms, or both. Three had had generalized convulsions. Later EEGs were normal in all. Nine patients had follow up for a mean of about 5 yr, without any recurrence or other seizures, and five were on no AEDs. Some patients had had childhood absence seizures with remissions of up to 50 yr. There were no reports of cognitive decline.

Agathonikou and colleagues evaluated ASE in 21 patients followed for different primary generalized epilepsy syndromes *(34)*. Clinical manifestations ranged from "clouding of consciousness" to deep stupor. Many had precipitants such as sleep deprivation or AED discontinuation. All had EEG confirmation. Many episodes ended with generalized convulsions. Immediate recurrences were common. With a mean follow-up of 5 yr, all but three patients had remissions from SE lasting at least 2 yr, and two thirds had complete seizure freedom in the last year of follow-up. Most were taking valproate. There is no mention of significant cognitive or other sequelae. From the initial population, up to half of patients with with perioral myoclonia and ("phantom") absences with generalized convulsions had episodes of SE, while only 7% of those with juvenile myoclonic epilepsy had episodes of ASE. This paper shows the value of understanding absence (and other) SE in the context of an epilepsy syndrome diagnosis whenever possible.

Most of the patients described in this section have had the typical clinical and EEG features of absence seizures and are thus considered to have "typical absence status epilepticus." The usual setting for "atypical" absence is in children with lower frequency repetitive discharges on EEG and Lennox-Gastaut syndrome. This may also recur, but any subsequent morbidity or cognitive decline is usually attributed to the underlying illness causing the syndrome, even when that cannot be identified well. The same applies to other atypical cases of absence status that occur in progressive epilepsy syndromes and those associated with storage diseases. Many of

Table 1
Morbidity in Absence Status Epilepticus

Status description	No. pts	Consequences
Spike wave stupor (1–2 d) *(26)*	6	Several recurrences No long-term sequelae noted
Absence SE *(27)*	38	Few with subsequent amnesia; uncertain duration "No clear prognostic significance"
"*De novo*" SE in the elderly *(32)*	11	No recurrences in 5-yr follow-up No sequelae noted
Typical absence syndromes *(34)*	21	Often situational (e.g., drug withdrawal) 5-yr follow-up: 69% seizure-free, 14% ASE recurrence No cognitive loss mentioned

these patients have generalized convulsions and other seizures. The other seizures and other aspects of the illness are thought to cause most of the morbidity. The effect of atypical ASE itself cannot be separated.

Overall, the reports cited in this section detail typical ASE in 76 patients (Table 1). No significant long-term morbidity was reported. All authors conclude that ASE confers little or no lasting harm. Of course, some patients with impaired responsiveness might suffer trauma during the SE, and some episodes recur. There is clearly long-term morbidity when absence SE occurs within conditions associated with neurologic impairment, such as Lennox-Gastaut syndrome and the progressive epilepsies, but the ASE itself does not appear to contribute significantly to that morbidity.

Patients with ASE as part of primary generalized epilepsies appear very likely to have recurrences, especially when AEDs are discontinued. In idiopathic ASE, recurrence is the rule in most patients until adequately treated *(35)*. Nevertheless, no patients appeared to suffer any significant long-term morbidity. The older patients with *de novo* SE often did not require long-term medication, and recurrence was less frequent; there was no apparent long-term morbidity, but follow up was not detailed extensively.

4.2. Complex Partial Status Epilepticus

Complex partial status epilepticus (CPSE) was reported infrequently until recently, perhaps because of the stringent definitions described in Chapter 2. Clinical manifestations include an "epileptic twilight state" with a lack of responsiveness, confusion, and bizarre, and particularly fluctuating, behavior *(36–39)*. Some cases constitute prolonged repetitive complex partial seizures, while others include continuous seizure activity (*see* Table 2).

While ASE often occurs in the setting of epilepsy as the only illness and almost never leads to long-term cognitive or other neurologic dysfunction (other than recurrent seizures), CPSE does not bode quite as well for the patient. Likely because of its association with vascular disease, focal lesions, and prior focal-onset seizures, CPSE is often harder to treat than ASE and appears more likely to lead to recurrences,

Table 2
Morbidity of Complex Partial Status Epilepticus

Status description	No. pts	Consequences
CPSE *(40)*	1	"Return to normal"
CPSE *(37)*	1	4 episodes (days long)/3 yr Severe recent memory loss lasting at least 3 wk
Children *(42)*	4	Subsequent normal development
CPSE *(39)*	2	Short term memory loss ≥4 mo One with generalized convulsions: "persistent" memory loss
CPSE *(38)*	8	Frequently recurrent; "return to baseline cognitive function"
CPSE in a child *(43)*	1	Recovered well after 2 mo SE
CPSE *(41)*	20	17 with recurrence None with cognitive deterioration (5 with neuropsychologic testing)
Frontal-onset CPSE *(44)*	10	9/10 normal neuropsych testing (1 syphilis); no recurrent SE on AEDs

of both seizures and other episodes of SE. Focal-onset seizures are manifestations of underlying lesions, and these are the major contributors to long-term neurologic dysfunction.

Some of the earliest reports of CPSE were extremely well-documented but included single cases—in part because the diagnostic criteria were so restrictive. A teenager reported by Engel and colleagues had recurrent episodes of fluctuating alteration in consciousness *(37)*. Postictally, amnesia lasted at least several weeks. Another child reported by Mayeux and Lueders had a hemianopia and prolonged confusion following a right frontal craniotomy and left body focal motor seizure *(40)*.

Most reports of CPSE state that the patients return to a normal condition, but not all have been studied thoroughly with neuropsychologic testing. Two patients reported by Treiman and Delgado-Escueta had prolonged memory loss following episodes of CPSE lasting from 1 to 4 h *(39)*. One deficit lasted at least 4 mo, and another was described as "persistent" although this patient also had generalized convulsions.

All eight patients evaluated by Ballenger and colleagues had had earlier seizures, and almost all had episodes of SE *(38)*. Most had variously impaired responsiveness and nonstereotyped automatisms, all associated with continuous ictal discharging activity. Those with recurrent seizures had more stereotyped automatisms. There was no formal neuropsychologic testing, but all eight patients "returned to baseline cognitive function" after the SE.

Most studies do not have prolonged and comprehensive follow-up in terms of neurologic or cognitive function. Follow-up was better in the series of Cockerell and colleagues covering 20 patients with CPSE *(41)*. All had focal-onset epilepsies. Most episodes persisted from a few days to a few weeks. Recurrent episodes of CPSE

were frequent (in 17 of 20) despite apparently reasonable AED treatment. Five patients had detailed neuropsychologic testing at least 2 yr after the episode, and none showed any decline on test scores.

Three of four children with NCSE (ages 1 to 4) evaluated by McBride and colleagues had recurrent seizures later, but development appeared normal in all *(42)*. One very interesting 11-yr-old boy had over 1 mo of complex partial SE and recovered 2 mo later but was entirely normal after a year *(43)*. This suggests that even with prolonged cognitive deficits, complete recovery is possible eventually.

Kaplan notes that CPSE can be subdivided by site of origin *(33)*. CPSE of frontal lobe origin may be more difficult to treat than that of temporal lobe origin. CPSE of frontal origin can be quite refractory to the usual intravenous benzodiazepine treatment; nevertheless, these patients did not have recurrences of SE although several had later seizures *(44)*. Underlying illness led to most of the morbidity, but there were no reports of persistent neurologic abnormalities.

In sum, of the 47 patients (at least without substantial comorbidity) described in papers from this section with any follow-up noted (Table 2), 5 had prolonged memory deficits that could have been the result of the CPSE itself. It is difficult to be certain that SE was the cause, but it is reason for concern and one of the many reasons for trying to interrupt CPSE expeditiously.

Though follow-up has been sparse in almost all series, there are few reported cases of persistent cognitive deficits attributable to episodes of CPSE. Impaired memory is by far the most common. If CPSE represents even one quarter of all cases of NCSE, and NCSE is one quarter of all SE, these patients with persistent deficits must represent a tiny fraction of all SE cases. Considering that under "a dozen documented cases demonstrate lasting cognitive sequelae" after what is estimated to be many thousands of cases, Kaplan concludes that there is very little long-term morbidity directly attributable to CPSE *(33)*.

With significant comorbidities, however, patients do not fare as well. Krumholz and colleagues reported a detailed study of 10 patients with CPSE for 36 h or more, all of whom had lasting neurologic deficits *(45)*. Two patients had strokes, two had encephalitis, and three had multiple medical problems that may have contributed to the deficits. Three patients had refractory epilepsy, and all had prolonged memory deficits, lasting 3, 6, and 24 mo. Two of these three had significant difficulties with attention and concentration for at least 3 mo, but at least two improved. Premorbid testing was not available, but the severe cognitive problems did not appear to predate the SE. This series and other individual reports *(37,39)* show that prolonged memory deficits can occur after NCSE. It is uncertain whether they are permanent. This study also noted that CPSE occurred more frequently in medically sick patients, raising the question of synergistic harmful effects of NCSE and medical illnesses. The diagnosis was often delayed, as was the response to appropriate medications even after the diagnosis.

4.3. Focal Nonconvulsive Status Epilepticus

There are very few cases reported with nonconvulsive forms of simple partial status epilepticus. Most of the reported focal SE is focal motor SE *(46)* or epilepsia

partialis continua (EPC). One of four patients with prolonged focal sensory NCSE lasting up to days was cured by surgery; others had recurrences, but no clear worsening of the illness was cause by the SE *(47)*. Patients with EPC usually have substantial underlying lesions that appear to account for the clinical, and pathologic, deficits *(48,49)*. Of course, EPC is not "nonconvulsive."

4.4. Other Nonconvulsive Status Epilepticus

Relatively few NCSE studies have been restricted to patients with pure ASE. Several more studies, usually with fewer patients, have included a careful diagnosis of CPSE. Most reports of NCSE do not specify clearly whether the patients have such relatively pure forms of NCSE. Other series, including several types of NCSE, contain more patients but with more heterogeneous populations. Several series show little long-term sequelae (Table 3). Most do not concentrate on long-term follow-up or assessment of residual morbidity.

Guberman and colleagues reported NCSE in 10 adults with generalized discharges, often with lateralizing features suggesting secondary generalization *(50)*. Nearly all responded quickly to intravenous benzodiazepines. Eight patients had follow-up for an average of 5.6 yr, and seven of these had several recurrences despite AEDs. They had "no evidence of long-term intellectual, memory, or behavioral deterioration." In 1985, Lee reported 11 patients with "late life onset" NCSE *(51)*. Discharges were generalized, but there was also evidence of focal onset. Patients were followed for up to 5 yr and were said to do well, but cognitive function was not assessed clearly. NCSE recurred in three and generalized convulsions in four, sometimes when medication was stopped.

The report of Scholtes and colleagues covered 65 patients with NCSE: 40 with CPSE and 25 with ASE *(46)*. Frequently, the clinical presentation did not distinguish between the two, although CPSE more often had focal clinical signs. Fluctuation of consciousness was actually more common in ASE, but these cases may not have been "classic" ASE. Almost all patients had earlier epilepsy, and almost all had a good outcome, with no lasting morbidity. Exceptions included an old man who died of aspiration pneumonia acquired during the CPSE and two others who had persistent cognitive abnormalities (of uncertain duration). More often, long-term morbidity was caused by underlying illnesses in the CPSE group.

The 32 patients with mixed types of NCSE described by Tomson and colleagues usually had histories of earlier epilepsy; most appeared to have seizure activity that was secondarily generalized from an initial focal onset *(31)*. Almost all responded immediately to intravenous benzodiazepines, but most had recurrences. No residual morbidity appeared, but follow-up was not reported.

Another group had predominantly ASE (18 of 22 cases), and the majority had earlier epilepsy *(52)*. There were many (usually medical) precipitants. Earlier psychiatric disorders and cerebrovascular disease complicated diagnosis. Most patients appeared confused or moderately unresponsive, but staring and myoclonic jerks were common. Most responded rapidly to intravenous benzodiazepines. Some did

Table 3
Morbidity of Nonconvulsive Status Epilepticus, Mixed Types

Status description	No. pts	Consequences
"Late life ictal confusion" *(51)*	11	"All did well;" followed up to 5 yr
NCSE *(50)*	10	Often recurrent 8 pts with 5-yr followup: no deterioration
Adults *(52)*	22	"Did well;" little followup
Mostly CPSE *(31)*	32	No sequelae noted.
40 CPSE, 25 absence *(46)*	65	Good outcome, except 1 died, and 2 with cognitive problems

well (with or without maintenance anticonvulsants), but few patients had long follow-up. Persistent morbidity was not reported.

The reports from this section cover 140 patients of mixed types of NCSE. Most had earlier epilepsy as the primary cause of NCSE, i.e., SE not due to a severe underlying medical illness. Few were followed for more than a few months, but almost none with long-term follow-up appeared to suffer persistent neurologic deficits attributable to the NCSE. Many had recurrent seizures or SE, and many had long-lasting morbidity due to underlying illness.

4.5. Generalized NCSE Associated With Severe Medical and Neurologic Illness

So far, we have dealt with forms of NCSE thought to arise from underlying epilepsies or noncatastrophic precipitants. In progressing from ASE through pure cases of CPSE attributable to long-standing epilepsy with precipitants, and then to more mixed forms of NCSE, the patient populations become more heterogeneous and include more underlying illnesses. Those comorbidities bear increasingly on the prognosis and longer-term morbidity. Progressing further along this continuum, there are many reports (often with even more patients) of NCSE in sick, hospitalized patients in the setting of severe underlying acute medical and neurologic illnesses. Often, this NCSE exhibits generalized epileptiform discharges on the EEG, but many have focal origins with subsequent generalization *(53)*. This NCSE is more worrisome when it occurs after generalized convulsions, after GCSE, or in the setting of major medical and neurologic disease. The topic of NCSE in sicker patients is a different category, sometimes referred to as "NCSE in coma," or "NCSE in the ICU," although not all patients are comatose or in the ICU.

Many of these patients are referred to as having electrographic status epilepticus (ESE)—the persistence of rapid, rhythmic epileptiform activity in patients with abnormal mental status. In the setting of serious medical illness, ESE has a poor prognosis. Nearly all such patients without known prior epilepsy have serious cerebrovascular or other acute illness. Outcome is often poor, but the persisting cognitive and other neurologic deficits or long-term harm are even more difficult to attribute to the SE because of the concomitant and severe underlying

Table 4
Nonconvulsive Status Epilepticus With Major Medical and Neurologic Illness

Status description	No. pts	Consequences
All types, NCSE *(58)*	101	27% mortality with acute medical illness 2 deaths possibly caused by NCSE
NCSE in the elderly *(61)*	24	52% mortality (of 25 episodes)
Electrographic SE *(55)*	48	Found by EEG, often in ICU. 88% mortality, esp. with coma, anoxia, mimimal with earlier epilepsy
NCSE in ICU *(62)*	23	57% mortality
'Nontonic-clonic' SE *(56)*	74	Found by EEG; 36% died, 19% deteriorated. 88% with epilepsy did well
NCSE in coma *(63)*	19	No clinical seizure, found by EEG. 47% died (same for coma without NCSE)
NCSE after SAH *(64)*	8	All died (from SAH)
"Subtle" SE *(65)*	134	VA study; no convulsions. 65% died, vs 27% with overt clinical GCSE

SE, status epilepticus; ICU, intensive care unit; NCSE, nonconvulsive status epilepticus; SAH, subarachnoid hemorrhage; GCSE, generalized convulsive status epilepticus.

illnesses *(54–57)*. Some authors do not even include these patients in a discussion of the consequences of NCSE.

Series of patients with generalized NCSE or ESE attributed to anoxia, multiple medical problems, or acute neurologic illness show high morbidity and mortality (*see* Table 4). The prognosis is determined primarily by the underlying illness—as it is for GCSE. In most reports of GCSE, the mortality is about 25% among all cases, but it is much higher for those with acute symptomatic SE, particularly when it involves anoxia or encephalitis, and particularly in older patients. NCSE in the same settings carries a similar high morbidity and mortality.

Mortality in NCSE was quite similar to that for SE overall in a series reported by Shneker and Fountain: of NCSE patients with acute medical illnesses, 27% died while just 3% with earlier epilepsy did (and that single patient had several medical illnesses) *(58)*. Two patients may have died due to the NCSE itself; the possibilities of arrhythmia, autonomic dysfunction, or sudden unexpected death in epilepsy were considered. Acute morbidity included respiratory dysfunction and infection, both attributed to the NCSE. Respiratory failure due to overtreatment with sedating medications was a possible contributor. Patients with these complications were much more likely to die. These complications may explain much of the morbidity and mortality of NCSE. Long-term cognitive sequelae were not evaluated. Some other patients with NCSE attributed to renal failure (with or without infections and antibiotics) did well with regard to seizures but suffered serious consequences of their medical illnesses *(59,60)*. In a series of elderly patients with NCSE, the majority died—even when anoxia was excluded *(61)*.

In one group of 48 patients with generalized electrographic SE, more than 80% died, including all those with anoxia or in coma *(55)*. Those with chronic epilepsy

and recent exacerbations fared well. Nonconvulsive or electrographic SE in comatose patients has a very high mortality *(54,55)*. Often, patients incur the morbidity of long ICU stays, as well. Of another 23 patients with NCSE in ICUs, 57% died *(62)*. In still another series of 74 patients with altered mental status found to have nontonic-clonic SE by EEG, 36% died and another 19% suffered long-term deterioration *(56)*. Nine did not respond to standard AEDs and required pentobarbital treatment. Medical and neurologic illnesses were the primary determinants of outcome; 88% of patients with earlier epilepsy returned to baseline.

In a study of 236 comatose patients with no overt clinical seizures, 19 (8%) were found to be in NCSE by EEG *(63)*. Hypoxia and anoxia were the most common causes. About half died. Interestingly, half the patients in coma *without* NCSE also died, suggesting again that the underlying illness contributed much more to the prognosis than did the NCSE.

NCSE or ESE may have an even higher mortality when it is unsuspected before the EEG findings. Of another 101 stuporous or comatose patients with subarachnoid hemorrhages, 26 had continuous EEG monitoring and eight of these had NCSE *(64)*. All eight died, with all deaths attributed to the hemorrhages. It was impossible to determine the effect of the NCSE itself.

Finally, in the large VA trial of comparative treatments for SE, most patients had overt GCSE, but others with "subtle" status and no convulsions (but rather twitching or blinking and EEG signs of ongoing status) had seizures that were extremely difficult to control *(65)*. Of 134 patients with subtle SE, 65% died, compared to 27% for patients with clinically evident GCSE. Only 8.8% were discharged from the hospital within 30 d. Most had life-threatening medical problems, 38% of them cardiac arrest.

Some have attempted to avoid the problem of SE in critically ill patients by declaring that SE in the setting of coma no longer constitutes status epilepticus. More reasonably, the underlying illness is the chief contributor to morbidity and outcome, but the SE is a manifestation of this underlying problem's effect on the brain and must be dealt with, recognizing that some treatment is unsuccessful. It is usually difficult or impossible to determine whether the SE contributes to the morbidity or mortality.

5. COGNITIVE COMPLICATIONS

There have been a few attempts to assess the long-term morbidity of status epilepticus. Most studies are pediatric and retrospective. Most cover GCSE, not NCSE. Several have found negative consequences of SE, but it is very difficult to control for many variables. Ideally, one would have comprehensive neurologic and neuropsychologic evaluations before and after SE. This is seldom available. Even when it is, there are additional problems in comparing the two evaluations. Patients will naturally worsen if there is a progressive illness, whether or not related to the SE. Also, many patients with neurologic deficits fluctuate with time; studies require more patients to control for this variation. Finally, it is difficult to control for the influence of AEDs. Medications may change after an episode of SE, and doses, serum levels, and drug interactions may change frequently in these patients with refractory epilepsy, including at the time of testing.

In one of the best attempts to address these concerns, Dodrill and Wilensky followed 143 adults with epilepsy, with neuropsychologic testing on all *(66)*. Nine patients had episodes of SE during the 5-yr interval between tests, four GCSE and five CPSE. SE patients were matched to epilepsy controls by age, educational background, and seizure control. By comparison, SE patients worsened neuropsychologically while some of the controls improved. The SE patients, however, had an average 14-point lower IQ score before the SE and were taking an average of 2.8 AEDs before the SE, compared to 1.7 for controls.

Stores and colleagues studied 50 patients referred to an epilepsy center because of behavioral problems, all of whom had episodes of NCSE lasting hours to weeks, often treated inadequately *(67)*. Some intellectual or educational deterioration occurred subsequently in 28, but most were diagnosed as mentally retarded and had refractory epilepsy. Eighteen patients had Lennox-Gastaut syndrome, and 13 had mixed seizure disorders, including myoclonic and astatic seizures. Maytal and colleagues studied 193 children with SE, almost all convulsive *(68)*. After the SE, 17 had cognitive and other deficits, usually attributed to an acute illness such as a stroke. Two patients had cognitive deficits attributed to SE, but both of these cases were retrospective and details of the SE were not available. They concluded that "the major neurologic sequelae are usually due to the underlying insult rather than to the prolonged seizure itself."

6. SUMMARY

The morbidity and outcome in different forms of NCSE depend primarily on the cause of the SE, whether that is the underlying epilepsy syndrome or the underlying acute medical or neurologic illness. Often, it is clear that the SE itself leads to no morbidity. In other cases, it is much harder to determine the cause of morbidity, if there is any.

There are several types of absence SE, but neither animal experimental models, human radiologic or pathologic studies, nor clinical series show any evidence of morbidity lasting longer than the episode itself. When ASE is due to some other cause, such as medication withdrawal, recurrences are infrequent. With idiopathic or genetic-based epilepsies of different types, the epilepsy syndrome determines the likelihood of recurrence. "Atypical" absence SE in the setting of chronic or progressive neurologic illnesses, such as Lennox-Gastaut syndrome and storage diseases, is generally thought to lead to no morbidity from the SE itself, but overall morbidity is substantial and the prognosis poor—determined by the underlying illness.

Complex partial SE implies a focal onset and subsequent involvement of bilateral structures mediating alertness or attention. CPSE is clearly *associated with* significant morbidity, likely because the focal lesion represents an illness with some lasting morbidity. Several cases of prolonged memory disturbance have been detailed. Morbidity and neuronal damage caused by the SE itself, however, are speculative and extremely difficult to be sure of. It is possible that some of the morbidity derives from the SE itself, as suggested by an apparent synergy between SE and vascular disease, at least in one large series *(69)*. Many large series of patients with NCSE include mixtures of absence and CPSE.

Finally, the NCSE that occurs in the setting of acute medical and neurologic illness has as its most severe form ongoing electrographic status epilepticus, usually in patients comatose because of the original illness. In this setting, morbidity is severe and outcome poor, but they still vary with the underlying illness. It is impossible to determine whether any of the morbidity or complications, while often major, are due to the SE itself.

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V Treatment

13

Treatment of Generalized Convulsive Status Epilepticus

Tina Shih and Carl W. Bazil

1. INTRODUCTION

Generalized convulsive status epilepticus (GCSE) is the most common type of status epilepticus and carries the greatest risk of morbidity and mortality *(1)*. It is a neurologic emergency requiring immediate evaluation and treatment. The traditional definition of GCSE requires continuous, repetitive seizure activity for at least 30 min, or two or more discrete seizures within a 30-min period without recovery of consciousness between attacks. The temporal marker of 30 min is arbitrary and not based on physiologic or clinical data *(2)*. Several epileptologists have proposed a "mechanistic" definition of GCSE: Most seizures stop spontaneously in 1 or 2 min; therefore, longer seizures generally reflect a problem with the usual mechanisms of seizure termination. The "mechanistic" definition refers to any seizure that will not terminate spontaneously, consisting of convulsive movements and loss of consciousness *(3,4)*. This definition, however, is not practical for clinical and research purposes because there is presently no clear way to distinguish a seizure that will terminate on its own from one that will not. An "operational" definition of GCSE must still be described in terms of time *(4)*.

Clinically, time is important in the management of GCSE, determining patient outcome and response to treatment. Although the underlying etiology of status epilepticus (SE) is the most important predictor of prognosis *(5–7)*, etiology is not mutable and usually not subject to intervention. Clinicians, however, may be able to shorten the duration of seizure activity, and duration may be the second most important factor influencing outcome *(1,8–10)*. There is considerable evidence that prolonged seizures may result in neuronal injury, cell death, or both, and this becomes most pronounced after an hour or more of continuous seizure activity *(11)*. In addition, animal and human data suggest that the earlier the therapeutic intervention, the more likely one can terminate the seizure *(7,10,12,13)*. One retrospective study demonstrated that SE could be terminated in 80% of patients who received "first-line" anticonvulsant medication within 30 min of onset. If first-line medication was started 2 h after onset, however, only 40% of patients responded *(7)*. Emerging consensus among clinicians is that any convulsive seizure exceeding 5 to 10 min, or any

From: *Current Clinical Neurology: Status Epilepticus: A Clinical Perspective*
Edited by: F. W. Drislane © Humana Press Inc., Totowa, NJ

attack that persists at the time of evaluation, should be considered probable GCSE requiring immediate therapy *(1–3,14)*.

2. TREATMENT GUIDELINES AND GENERAL PRINCIPLES

As in any emergency, the evaluation and treatment of GCSE must be conducted simultaneously. Management of GCSE should take into consideration four main goals: (1) termination of GCSE; (2) prevention of seizure recurrence once GCSE is terminated; (3) determination and management of the underlying etiology; and (4) treatment of complications of GCSE *(2,15)*. This chapter will review current perspectives and supporting data on the treatment of SE. It will also touch on the determination of etiology and prevention of recurrences.

Airway, breathing, and circulation (ABCs) must be addressed immediately (*see* Table 1). Initial studies include glucose, serum chemistries (most importantly sodium, magnesium, calcium, phosphate, BUN), arterial blood gas, antiepileptic drug levels (if applicable), complete blood count, and urine and serum toxicology. Fever, hypoglycemia, hypoxemia, hypotension, and other metabolic abnormalities should be treated concurrently. In infants less than 24 mo of age, intravenous pyridoxine (100–200 mg) should be considered. Although pyridoxine deficiency is a rare cause of SE, the diagnosis is made only by observing the EEG and clinical response to test doses.

Pertinent history should be obtained, including any recent change in medication, alcohol or drug use, history of epilepsy, previous brain injury, or recent illness. One urban study determined that drug overdose (from illicit street drugs or prescribed medications) was the underlying cause of GCSE in 50% of patients who did not have a history of seizures *(7)*. In this setting, gastric lavage and intravenous antibiotics should be considered in the emergency room.

A lumbar puncture to examine the cerebrospinal fluid should be contemplated, especially in patients with fever. Infection accounted for approximately one-third of cases of SE in adults in one community-based study *(16)*. Brain imaging (CT or MRI) should also be performed in most patients at some point in the evaluation, especially if there is no history of epilepsy or other clear reason for seizures.

EEG monitoring is mandatory for any individual who has not regained consciousness quickly after the motor manifestations of seizures have ceased or who has received a relatively long-acting paralytic agent *(14,17)*. In one retrospective study using continuous EEG monitoring, 48% of patients continued to manifest electrographic seizures after clinical seizure activity had stopped, with 14% in nonconvulsive SE *(18)*. Bleck recommends continuous EEG monitoring for all patients who manifest seizure activity after treatment with first- and second-line agents *(2)*. Not all hospitals have the capacity to perform this service at all times, but a routine EEG should be performed as soon as possible. Even so, the manner in which these EEG results are used in the management of GCSE is still being defined in the literature and in clinical practice. A wide range of EEG abnormalities has been described in patients with SE *(19,20)*, but these findings are often poorly understood, and interpretation is heavily debated. Hirsch and Claassen have identified stimulus-responsive

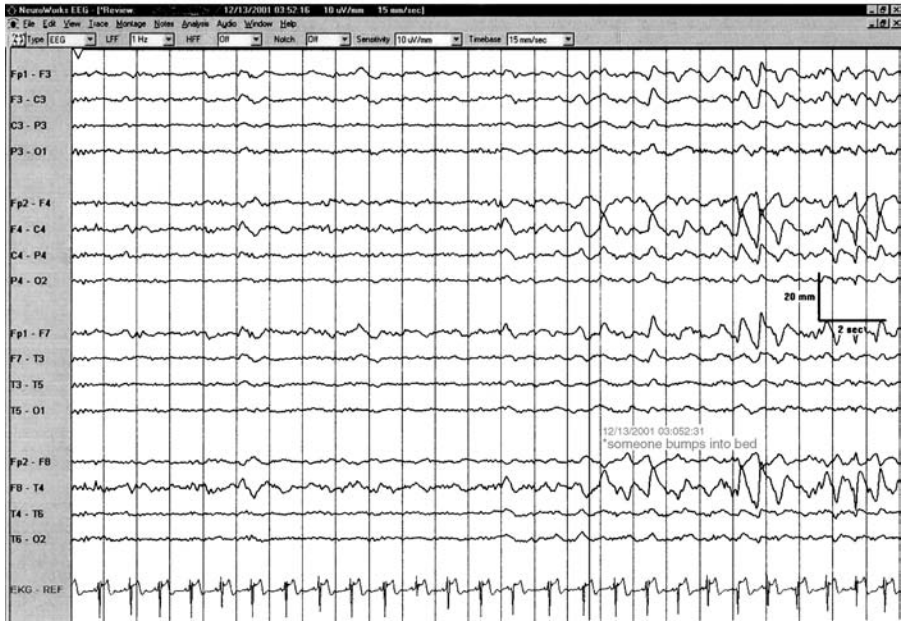
Table 1
In-Hospital Treatment Protocol for Generalized Convulsive Status Epilepticus in Adults

Time	Action
0–5 min	Diagnose; give O_2, ABCs with frequent vital sign monitoring; obtain iv access; begin EKG monitoring; draw blood for CBC, sodium, glucose, magnesium, calcium, phosphate, LFTs, AED levels, ABG, toxicology screen. Treat with thiamine 100 mg iv with 50 mL of D50 iv.
6–10 min	**Lorazepam 4 mg iv** over 2 min. If seizures persist, repeat in 5–10 min. If patient not already intubated, consider rapid sequence induction with endotracheal intubation.
10–20 min	**Fosphenytoin 20 PE/kg iv** at 150 PE/min, with blood pressure and EKG monitoring.
20–60 min	If seizures persist, give one of the following (intubation necessary with all medications except valproate): **civ midazolam:** Load 0.2 mg/kg; repeat 0.2–0.4 mg/kg boluses every 5 min until seizures stop, up to a maximum loading dose of 2 mg/kg. Initial civ rate 0.1 mg/kg/h. Continuous intravenous dose range 0.05–2 mg/kg/h. If seizures persist, proceed to pentobarbital. **civ propofol:** Load 1 mg/kg, repeat 1–2 mg/kg boluses every 3–5 min until seizures stop, up to a maximum loading dose of 10 mg/kg. Initial civ rate 2 mg/kg/h. Continuous intravenous dose range 1–15 mg/kg/h. If seizures persist, proceed to pentobarbital. **iv valproate:** 40 mg/kg over approx 10 min. If seizures persist, 20 mg/kg over approx 5 min. If seizures persist, proceed to civ midazolam or propofol. **iv phenobarbital:** 20 mg/kg iv at 50–100 mg/min. If seizures persist, proceed to civ midazolam, propofol, or pentobarbital.
>60 min	**civ pentobarbital:** load 5–10 mg/kg up to 50 mg/min. Repeat 5 mg/kg boluses until seizures stop. Initial civ rate: 1 mg/kg/h; civ dose range: 0.5–10 mg/kg/h. Traditionally titrated to burst suppression on EEG. Begin EEG monitoring ASAP if patient does not awaken rapidly or if any civ treatment is used.

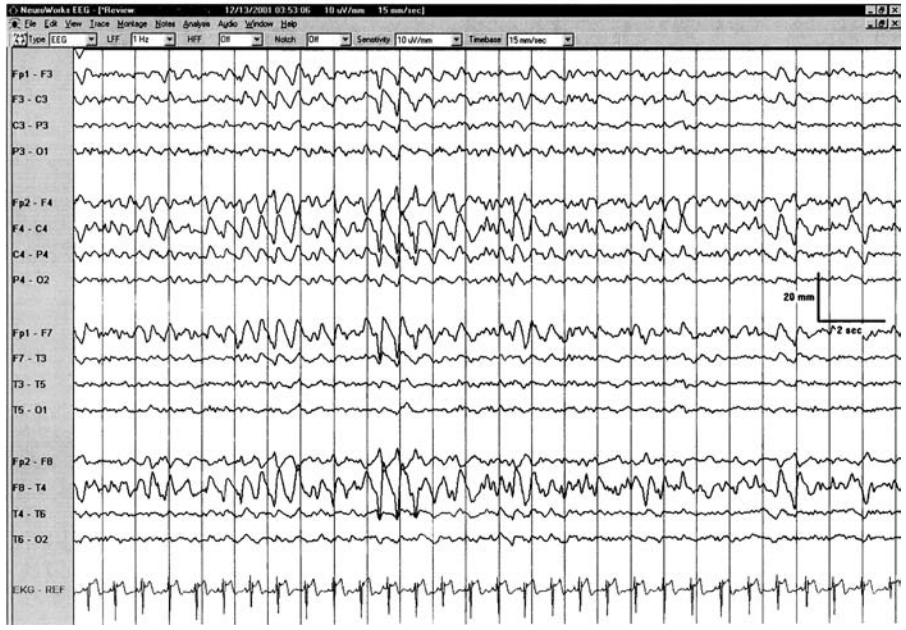
ABCs, airway, breathing, circulation; iv, intravenous; EKG, electrocardiogram; CBC, complete blood count; LFTs, liver function tests; AED, antiepileptic drug; ABG, arterial blood gas; D50, 50% dextrose; civ, continuous intravenous; EEG, electroencephalograph; PE, phenytoin equivalents. Adapted from ref. *14*.

periodic discharges in many monitored comatose patients, further complicating the picture (*see* Fig. 1A–C). Because of the ambiguity of some findings, they recommend close communication between the clinicians and the electroencephalographer when continuous EEG is used to direct management *(14)*.

A


Fp1 - F3
F3 - C3
C3 - P3
P3 - O1
Fp2 - F4
F4 - C4
C4 - P4
P4 - O2
20 mm
2 sec
Fp1 - F7
F7 - T3
T3 - T5
T5 - O1
12/13/2001 03:052:31
*someone bumps into bed
Fp2 - F8
F8 - T4
T4 - T6
T6 - O2
EKG - REF

B


Fp1 - F3
F3 - C3
C3 - P3
P3 - O1
Fp2 - F4
F4 - C4
C4 - P4
P4 - O2
20 mm
2 sec
Fp1 - F7
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F8 - T4
T4 - T6
T6 - O2
EKG - REF

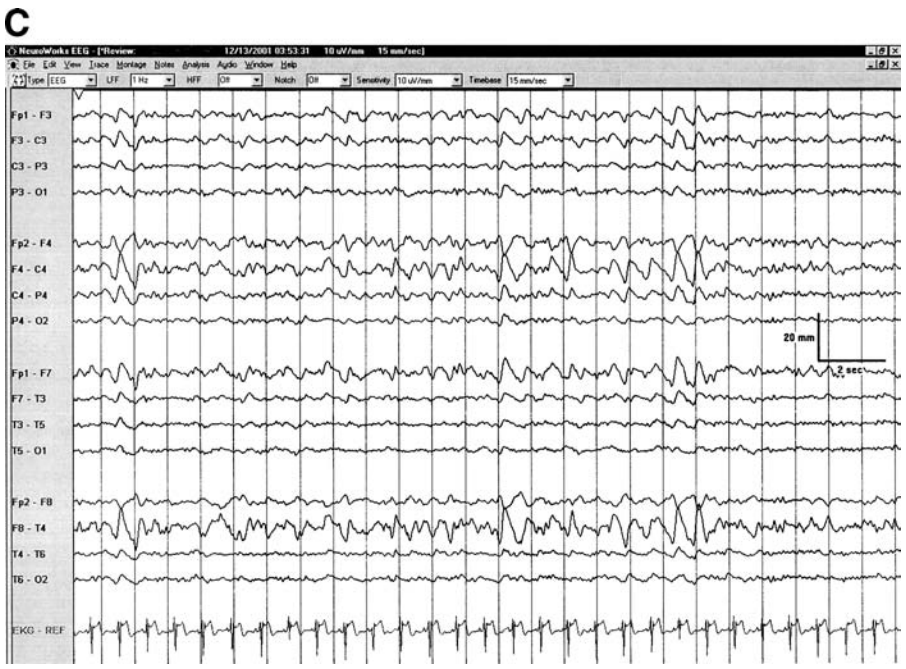


Fig. 1. Three consecutive pages of continuous EEG in a 57-yr-old woman with a history of a subarachnoid hemorrhage, grade III, and vasospasm on angiography. Stimulation (center right of first page) elicited periodic lateralized epileptiform discharges over the right parasagittal channels, which appeared to evolve in amplitude and frequency, to a maximum periodicity of 2 Hz. (Montage: longitudinal bipolar. Sensitivity 10 (μV/mm, LFF 1 Hz, HFF 70 Hz, timebase 15 mm/8) (Courtesy of Dr. Lawrence J. Hirsch.)

Treatment of status epilepticus is largely pharmacologic. Characteristics of the ideal medication would include (1) termination of all seizures immediately, (2) rapid and easy administration through any parenteral route without the need for special equipment, (3) rapid establishment of therapeutic levels in the central nervous system (CNS), and (4) absence of any adverse side effects (most importantly, respiratory depression or sedation) *(8)*. Currently, only three agents used in the treatment of chronic epilepsy may be given parenterally (phenobarbital, phenytoin, and valproic acid), and none of the available medications fulfills all these criteria.

As a result, most consensus recommendations have minimized the importance of the particular anticonvulsant used for GCSE. Instead, they have emphasized early and rapid treatment and the development of a treatment protocol *(1)*. Sperling wrote that "every individual or hospital should establish a standard treatment protocol for SE, for a familiar regimen has a greater chance of success" *(21)*. One retrospective nursing study confirmed this opinion; the time to terminate SE was shortened by an average of 235 min ($p = 0.026$) after development of a protocol *(22)*.

3. PHARMACOLOGIC THERAPY

3.1. Out-of-Hospital Treatment

Because rapidity of treatment is an important factor in the outcome of GCSE *(7,12)*, several prospective studies have focused on out-of-hospital treatment. The clinical scenarios studied are varied and have included caregiver-delivered treatment in the home, nursing-administered medication in institutions, and emergency medical technician (EMT)-administered treatment in the field. Because benzodiazepines have been recommended in the initial treatment of acute seizures *(1)*, most studies have focused on the three most widely available benzodiazepines in the United States—diazepam, lorazepam, and midazolam. Another important consideration has been the development of alternative means of administering medication when venous access is not possible or when nonmedical caregivers are involved. Although alternative routes (intranasal, rectal, buccal, and intramuscular) have been shown to be both safe and effective in the treatment of SE, acute repetitive seizures, or both, rectal diazepam gel (Diastat, Xcel Pharmaceuticals, San Diego, CA) is the only delivery system currently approved by the US Food and Drug Adminstration (FDA).

The route of administration frequently determines the clinical setting in which a medication may be given. Intravenous (iv) medications can be delivered only by trained personnel, typically paramedics. Others may be trained to administer drugs intramuscularly. In contrast, most caregivers can be taught to give medication through buccal, intranasal, or rectal routes, allowing medication to be given faster and, in some cases, avoiding the need for intervention by medical personnel.

3.1.1. Rectal Diazepam

Diazepam is highly lipid-soluble, allowing rapid absorption through mucosal membranes and penetration into the CNS. Peak plasma levels are achieved 10 to 60 min after rectal administration *(23,24)*. Bioavailablity has been reported to range between 81 and 98% *(24)*.

Two multicenter investigations studied the efficacy of rectal diazepam gel for the treatment of acute repetitive seizures *(25,26)* (*see* Fig. 2A,B). A total of 215 children and adults were randomized to receive either rectal diazepam or placebo. Doses were determined by weight (0.2–0.5 mg/kg of rectal gel, in 1 to 3 doses) and delivered at home by caregivers. The primary outcome measures for both studies were seizure frequency and probability of seizure freedom over 12 to 24 h of observation. Rectal diazepam reduced the number of recurrent seizures significantly in both studies. In the North American Diastat Study Group investigation, 55% of patients who received rectal diazepam were seizure-free, compared to 34% who received placebo ($p = 0.03$) *(26)*. Dreifuss and colleagues reported similar results, with seizure termination in 64% of patients given rectal diazepam and 24% with placebo ($p < 0.001$) *(25)*. There was no significant difference in rates of adverse effects in the two groups. Both studies concluded that rectal diazepam was safe and effective when given outside of the hospital for treatment of acute repetitive seizures.

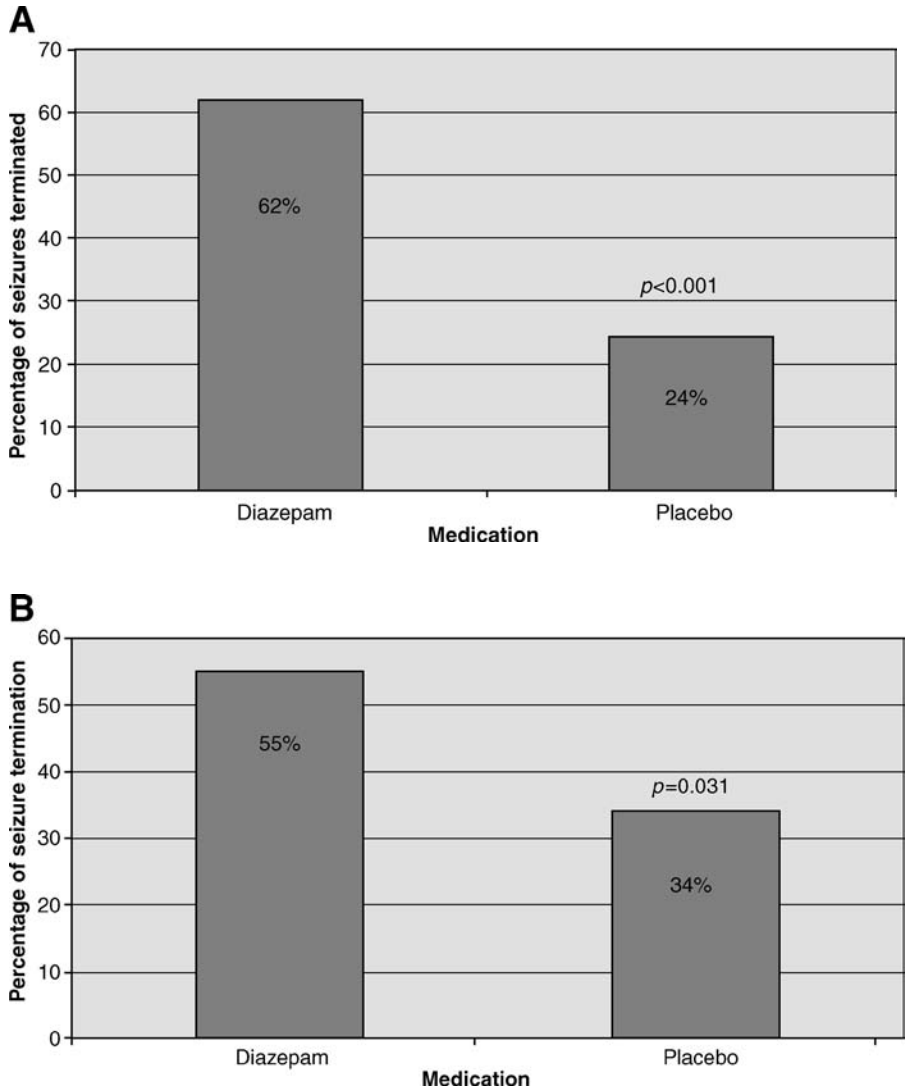


Fig. 2. Results from two randomized, placebo-controlled trials comparing rectal diazepam gel to placebo in children and adults. **(A)** Data adapted from *(25)*. **(B)** Data adapted from *(26)*.

In the third randomized, placebo-controlled investigation involving rectal diazepam, nurses administered either rectal diazepam (20 mg) or placebo to 22 institutionalized adults with severe epilepsy and frequent seizure clusters *(27)*. Eighty percent of seizure-cluster episodes were controlled over a 24-h period with rectal diazepam, while only 22% were terminated with placebo ($p < 0.001$).

3.1.2. Intramuscular Midazolam

Unlike lorazepam or diazepam, midazolam has properties that make it ideal for intramuscular administration. Its benzene ring is open in an acidic pH, allowing it to be water-soluble and thus absorbed rapidly from injection sites. On exposure to the slightly basic physiologic pH of the bloodstream, midazolam's benzene ring closes, and it becomes lipid-soluble, thereby entering the brain quickly *(28)*. When delivered intramuscularly, midazolam has a rapid onset of action. In 40 healthy adult volunteers, peak serum concentrations were achieved within 23 to 41 min following a single 7.5-mg injection *(29)*. Bioavailability averaged 87% in adult epileptic patients *(30)*.

In contrast, diazepam's lipid solubility causes it to be absorbed slowly and irregularly after intramuscular administration. In addition, a significant portion of the active drug precipitates locally *(28)*. Lorazepam is also absorbed slowly when injected intramuscularly. The time to peak plasma concentrations of diazepam and lorazepam may be as long as 90 min after intramuscular injection *(31,32)*. Because of this delay, intramuscular diazepam and lorazepam are not recommended in the treatment of SE *(1)*.

There is only one randomized, controlled investigation of the efficacy and safety of intramuscular midazolam for acute seizures. In this emergency room-based study, it was compared to intravenous diazepam in children with prolonged acute motor seizures. Although the two medications were equally effective at stopping seizures, patients in the midazolam group received medication significantly sooner than those receiving diazepam, resulting in faster seizure termination (7.8 vs 11.2 min, p = 0.047) *(33)*. The delay with diazepam was primarily due to difficulty obtaining iv access in patients with motor seizures.

In an extensive review of the literature, Towne and DeLorenzo summarized the results of many reports of children and adults (totaling 91 patients) who received intramuscular (im) midazolam (dose range 0.07 to 0.3 mg/kg) for acute seizures *(28)*. It was effective in terminating more than 90% of seizures, with seizures ceasing on average 2 to 3 min after administration *(28)*.

3.1.3. Buccal Midazolam

Another formulation is liquid midazolam applied over the gums. The mouth provides a large surface area of rich vascularization, allowing for rapid absorption systemically and avoiding first-pass metabolism *(34)*. Buccal midazolam has rapid CNS effects in healthy volunteers, with electroencephalographic changes evident within 5 to 10 min of administration *(34)*.

In the one randomized, controlled study of buccal midazolam *(35)*, 28 institutionalized young adults (with severe symptomatic generalized epilepsies) with continuous seizures lasting more than 5 min received either liquid midazolam (10 mg) over the gums or rectal diazepam gel (10 mg). The primary outcome measure was cessation of seizures within 10 min. There was no significant difference between buccal midazolam (75% efficacy) and rectal diazepam (59%; p = 0.16). No adverse effects were reported. The authors endorsed the use of buccal midazolam over rectal diazepam, citing buccal administration as easier and more acceptable socially.

3.1.4. Intranasal Midazolam

The nasopharynx also provides a large mucosal surface area, allowing rapid absorption and avoidance of first-pass metabolism *(36)*. Intranasal midazolam was used initially as an anesthetic agent in children and was safe and effective *(37)*. Its pharmacokinetic profile suggests that it may be an appropriate treatment for SE. Peak plasma concentrations are reached approx 14 min after administration *(36)*. Bioavailability is high, approx 85%, as opposed to the oral availability of midazolam, reported at around 50% *(36)*. There are also reports that acute seizures can be terminated within 3.5 min after intranasal midazolam *(38)*.

There are prospective data supporting intranasal midazolam. In one randomized, controlled study, 44 children (ages 6 mo to 5 yr) with febrile seizures lasting at least 10 min received intranasal midazolam (0.2 mg/kg) or intravenous diazepam (0.3 mg/kg) in a pediatric emergency room *(37)*. The two treatments were equally effective at controlling seizures (88% of episodes controlled with midazolam vs 92% with diazepam), but the mean time from arrival in hospital to seizure control was shorter with midazolam (6.1 min) than with diazepam (8.0 min; $p < 0.001$) *(37)*. No significant adverse effects were reported in either group.

In an uncontrolled study, intranasal midazolam (5–10 mg, depending on weight) was administered to 22 adults and children for 84 separate episodes of acute motor seizures *(39)*, terminating 79 of 84 seizures. Three of five treatment failures were due to poor technique in delivering midazolam. No adverse effects were reported.

3.1.5. Intravenous Lorazepam and Diazepam

One of the most important out-of-hospital status epilepticus studies was a San Francisco trial of intravenous benzodiazepines administered by paramedics *(40)*. This study was randomized, double-blind, and placebo-controlled. Intravenous lorazepam (2–4 mg), intravenous diazepam (5–10 mg), or placebo were administered to 205 adults with generalized tonic-clonic (GTC) seizures lasting 5 min or longer, or with repetitive GTC seizures without recovery of consciousness. A primary outcome measure was termination of SE by arrival in the emergency room. Benzodiazepines were clearly more effective than placebo at terminating SE. Fifty-nine percent of lorazepam patients were no longer in status when they arrived at the emergency room, compared to 42.6% with diazepam and 21.1% with placebo (odds ratio [OR] of lorazepam effectiveness vs placebo 4.8 [95% confidence interval {CI} 1.9 to 13.0]; OR of diazepam vs placebo 2.3 [95% CI 1.0 to 5.9]) *(40)*. Although not statistically significant, there was a trend favoring lorazepam over diazepam *(40)*. The rate of cardiorespiratory complications was not significantly different in any treatment arm (10.6% for lorazepam, 10.3% for diazepam, 22.5% for placebo) *(40)*. The authors concluded that benzodiazepines are safe and effective when administered by paramedics for out-of-hospital SE in adults *(40)*. They recommended iv lorazepam over diazepam *(40)*. Storage of iv lorazepam, however, requires refrigeration. The authors recommended that vials should be replaced every 60 d in warmer climates *(40)*.

3.2. In-Hospital Treatment

Once a patient arrives in the emergency room in the midst of a generalized convulsive seizure, the physican should consider the patient to be in GCSE. The protocol in Table 1 is used for adult patients at New York Presbyterian Hospital, Columbia University. This section provides an overview of agents used in the treatment of GCSE (*see* Table 2), divided into first-, second-, and third-line agents (lorazepam and diazepam; phenytoin, fosphenytoin, and valproate; and phenobarbital, respectively), all given intravenously. All doses apply to adults unless otherwise specified. The use of continuous iv propofol, midazolam, and pentobarbital will be covered in Chapter 14.

3.2.1. First-Line Agents: Lorazepam and Diazepam

Benzodiazepines are currently considered the most effective drugs for the treatment of status epilepticus *(1,41)*. In a review of uncontrolled studies, Treiman noted that 79% of SE cases (1063 of 1346 patients) were treated successfully if the first agent was a benzodiazepine (clonazepam, diazepam or lorazepam) *(41)*. One of the first prospective studies demonstrated that both lorazepam and diazepam controlled GCSE in 82% of cases, without significant difference in efficacy or safety *(42)*. Historically, diazepam had been the most extensively used medication for SE since its introduction in 1965 *(43)*. Largely as a result of the Veterans Affairs study *(10)*, however, lorazepam is now preferred for first-line treatment *(44)*.

The Veterans Affairs Status Epilepticus Cooperative Study was the first that provided definitive direction for initial treatment of GCSE. Three hundred eighty-four patients in overt GCSE were randomized to one of four treatment arms: lorazepam (0.1 mg/kg), phenobarbital (15 mg/kg), diazepam (0.15 mg/kg) plus phenytoin (18 mg/kg), or phenytoin alone (18 mg/kg) *(10)*. The primary outcome measure was the percentage of cases where treatment resulted in cessation of both motor and electroencephalographic seizure activity within 20 min after beginning drug infusion—with no recurrence of seizure activity over the next 40 min *(10)*. Lorazepam stopped SE in 65% of cases, phenobarbital 58%, the diazepam and phenytoin combination 56%, and phenytoin alone 44% (*see* Fig. 3) *(10)*. Overall, lorazepam was most successful ($p = 0.02$) *(10)*. The pairwise comparison of lorazepam versus phenytoin was also significant ($p = 0.002$); other pairwise comparisons were not. Lorazepam is easier to administer than the other agents; it can be delivered as a bolus, requiring the least time to infuse. Because of these data, the study recommended lorazepam as the best initial therapy for GCSE *(10)*.

Intravenous lorazepam has many qualities that explain its success in treating GCSE. Its median latency of action is between 3 and 11 min *(42,45)*. Lorazepam is bound tightly to the $GABA_A$ receptor complex *(45)* and has a small volume of distribution of unbound drug *(41)*; therefore it has a long duration of action, on the order of 12 to 24 h *(45)*. Because of this prolonged effect, Lowenstein and Alldredge suggested that no additional treatment may be necessary in many cases of SE, especially if the underlying diagnosis is known and the duration of the provoking factor causing seizures is brief *(17)*. For most adults, the typical loading dose of lorazepam is 4 to 8 mg (0.5–0.1 mg/kg) *(10,42,45)*.

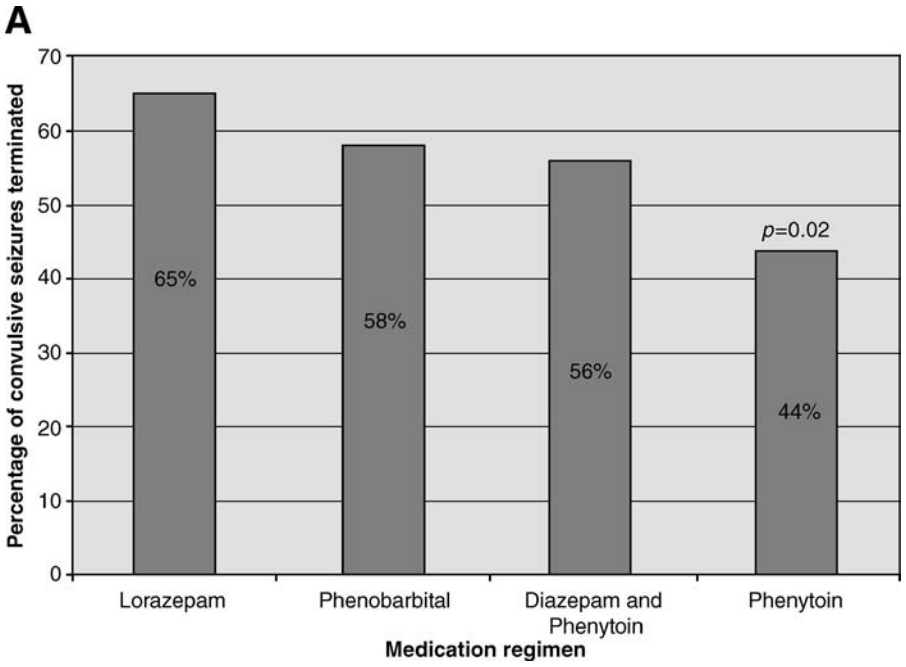
Table 2
Comparison of Anticonvulsant Medications Used in Status Epilepticus

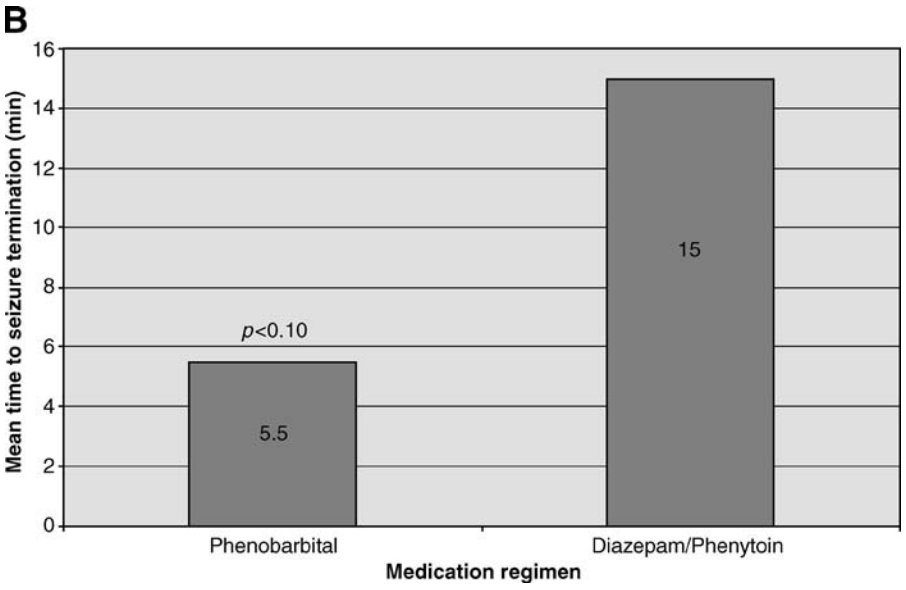
Medication	Route of delivery	Latency of action (min)[a] (ref)	Duration of effect (h) (ref)	Adverse effects	Class I evidence?
Lorazepam	Intravenous	3–10 *(42)*	12–24 *(45)*	Respiratory depression, sedation, hypotension	Yes
Diazepam	Rectal	5–15 *(96)*	<1 *(96)*	Sedation	Yes
Diazepam	Intravenous	1–5 *(42)*	<1 *(43)*	Respiratory depression, sedation, hypotension	Yes
Midazolam	Intramuscular	5–10 *(33)*	<1 *(33)*	Sedation	Yes
Midazolam	Buccal	5–10 *(35)*	<1 *(35)*	Sedation	Yes
Midazolam	Intranasal	<5 *(36)*	<3 *(36)*	Sedation	Yes
Phenytoin	Intravenous	10–30 *(53)*	12–24 *(52)*	Hypotension, cardiac arrhythmias, purple glove syndrome	Yes
Fosphenytoin	Intravenous	10–30 *(63)*	12–24 *(63)*	Paresthesias, cardiac arrhythmias	No
Phenobarbital	Intravenous	5–30 *(58)*	48–72 *(58)*	Respiratory depression, sedation, hypotension	Yes
Valproate	Intravenous	<20 *(70)*	8–24 *(70)*	Nausea, taste perversion, injection site reactions	No

[a]Based on time to stop status epilepticus or prolonged seizures.

Intravenous diazepam enters the CNS even more quickly than lorazepam; maximum brain concentrations occur within 1 min after infusion in animal studies *(46)*. Median onset of action is between 2 *(42)* and 15 min *(47)*. Nevertheless, CNS and plasma levels fall by about two thirds in the first 2 h after administration, primarily because of its large volume of distribution *(48)*. With a 0.3 mg/kg iv bolus dose of diazepam, its duration of action in controlling SE is less than 50 min *(43)*. Seizure recurrence is frequent when diazepam is used as a single agent *(1,45,48)*. When 100 cases of SE were reviewed, seizure control was maintained in only 38% with diazepam as the initial agent *(49)*. If diazepam is the initial treatment, a longer-acting medication such as fosphenytoin should also be administered to prevent seizure recurrence *(1)*. For most adults, the loading dose of iv diazepam is 10 to 20 mg *(10,42)*.

The most common adverse effects of benzodiazepines are respiratory depression and systemic hypotension, both dose-related. A less common adverse effect is cardiac arrhythmias. From the three in-hospital prospective studies, the rate of adverse effects has been between 12 and 53% *(10,42,47)*.


A
Percentage of convulsive seizures terminated
70
60
50
40
30
20
10
0
65%
58%
56%
44%
p=0.02
Lorazepam
Phenobarbital
Diazepam and Phenytoin
Phenytoin
Medication regimen


B
Mean time to seizure termination (min)
16
14
12
10
8
6
4
2
0
p<0.10
5.5
15
Phenobarbital
Diazepam/Phenytoin
Medication regimen

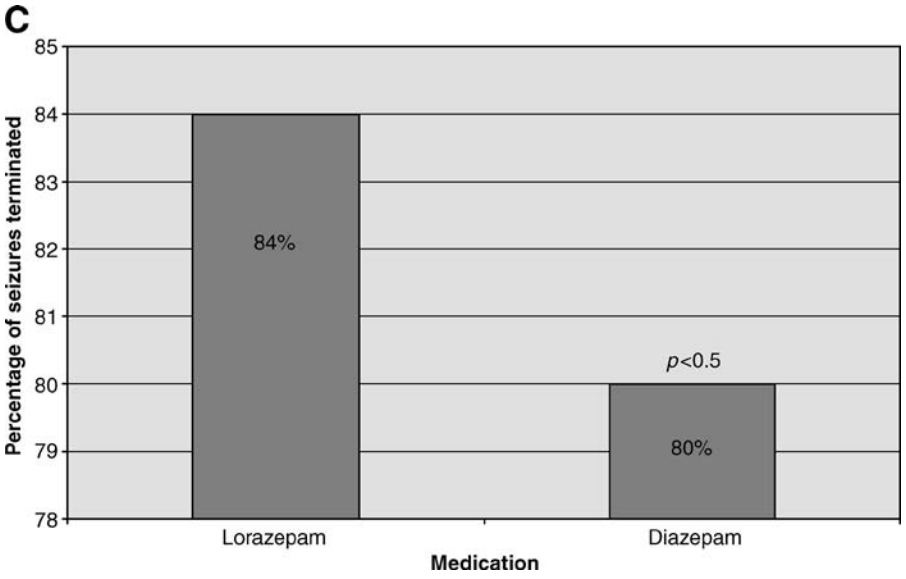


Fig. 3. Data from the only prospective, randomized, in-hospital trials directly comparing treatment strategies for generalized convulsive status epilepticus (GCSE). **(A)** Overall, lorazepam was significantly more successful in the treatment of GCSE ($p = 0.02$). Data adapted from ref. *10*. **(B)** Median time to seizure termination was significantly shorter for patients treated with phenobarbital, compared to patients treated with diazepam/phenytoin ($p < 0.10$). Data adapted from ref. *47*. **(C)** Leppik and colleagues did not find any significant difference between lorazepam and diazepam in the treatment of GCSE. Data adapted from ref. *42*. Note: bars are not proportional; the *y*-axis runs 78 to 85%.

3.2.2. Second-Line Agents: Phenytoin, Fosphenytoin

Although there are no prospective data determining the most appropriate second-line therapy *(14)*, phenytoin and fosphenytoin (a phenytoin prodrug) are typically recommended if lorazepam fails to terminate GCSE. Data from the VA cooperative study suggest, however, that this approach may be flawed *(10)*. In this cohort, if the initial medication failed to terminate SE, the aggregate response rate to second-line agents was 7.0%, and to third-line agents 2.3% *(2)*. This low success rate may be due in part to a significant delay in treatment in the VA cohort. In a more recent retrospective review, phenytoin or fosphenytoin were effective in 66% of cases of SE, possibly because they were used earlier *(13)*.

3.2.2.1. iv Phenytoin

Before the VA cooperative study, iv phenytoin was frequently a first-line agent and has been used widely for SE since 1956 *(50)*. Its relative efficacy in SE was demonstrated in several studies: between 40 and 90% of cases of GCSE or repetitive acute

seizures terminated with iv phenytoin *(10,51–53)*. In addition, iv phenytoin stops seizures without depressing consciousness *(51)* and could thus avoid the need for endotracheal intubation or extended critical care.

Phenytoin's pharmacokinetic profile has favorable features in the treatment of GCSE. Animal studies showed brain concentrations peaking within 10 min of iv administration *(46)*, and an anticonvulsant effect occurs within 3 min *(54)*. Nevertheless, phenytoin is less lipid-soluble than benzodiazepines and its latency of action is longer *(1)*. This delay may be attributed to the time it takes for plasma/CNS equilibration, which does not occur until 50 min after a 14 mg/kg iv loading dose *(52)*.

Although there is delay in its initial anticonvulsant activity, phenytoin retains its anticonvulsant effect for up to 12 h after infusion *(51,52,55)*, attributed largely to its high CNS levels and tight binding to brain tissue. Brain parenchyma concentrations of phenytoin following rapid intravenous infusion are greater than serum concentration within 20 min *(52)*. Brain parenchyma concentrations remain between 4 and 10 times the serum free (unbound) concentrations under ordinary clinical circumstances *(56)*, possibly due to both phospholipid and protein binding *(56)*.

In trials of iv phenytoin for GCSE, loading doses have generally ranged between 13 and 18 mg/kg *(10,47,52,53)*. Most authors recommend 18–20 mg/kg loading doses for adults, while 15 mg/kg has been recommended for elderly patients *(1)*. Most adults have serum concentrations greater than 10 μg/mL up to 24 h after a loading dose of 18 mg/kg. If the iv loading dose is 12 or 15 mg/kg, however, serum levels fall below therapeutic levels within 24 h *(53)*. This study reported no significant adverse effects with the higher loading dose, even in patients with chronic phenytoin exposure. Serum drug levels should be monitored closely in all patients treated for SE; in this population, serum phenytoin half-lives vary considerably (between 15 and 100 h) *(53)*. Furthermore, if there is hypoalbuminemia, renal insufficiency, or concomitant treatment with other highly protein-bound medications such as valproate or benzodiazepines, daily serum free unbound phenytoin levels should be obtained. During and after SE, such levels should be maintained at 1.5 to 2.5 μg/mL, equivalent to total serum phenytoin levels of 15 to 25 μg/mL if protein binding is normal *(14)*.

The main limitations of iv phenytoin have to do with the vehicle required to dissolve this very poorly soluble compound. It includes 40% propylene glycol, 10% ethanol, and has a pH of 12 *(57)*. The vehicle increases the risk of hypotension and is associated with considerable local irritation and even tissue necrosis if subcutaneous extravasation occurs. As a result, phenytoin must be infused slowly, at a maximum rate of 50 mg/min. For a typical 70-kg adult patient, complete infusion of an adequate loading dose takes at least 28 min, compared to the 1-min infusion of diazepam or lorazepam. In clinical practice, iv phenytoin administration is often prolonged further, as the infusion may be slowed or halted because of hypotension, cardiac arrhythmias, or local irritation or phlebitis requiring change of the iv line *(53)*. Thus, the utility of iv phenytoin in SE is limited by its physical properties (chiefly the vehicle) and risks of adverse effects *(8)*.

3.2.2.2. iv Fosphenytoin

In 1996, the phenytoin prodrug, fosphenytoin, was introduced in the United States. Fosphenytoin is the disodium phosphate ester of 3-hydroxymethyl 5,5-

diphenylhydantoin. Because of the phosphate ester group, there is a difference in the molecular weights of fosphenytoin and phenytoin; 75 mg of fosphenytoin sodium is the molar equivalent of 50 mg of phenytoin sodium *(58)*. Thus, for the same pharmacodynamic effect as a typical adult dose of intravenous phenytoin (e.g., 300 mg), a 50% larger dose of fosphenytoin (e.g., 450 mg) must be administered. To avoid confusion in administration, fosphenytoin doses are prescribed as "phenytoin equivalents" (PE), i.e., the dose of phenytoin delivered after conversion.

Fosphenytoin has several advantages over phenytoin:

1. Fosphenytoin can be easily and rapidly delivered intravenously (up to 150 PE/min, in comparison to phenytoin at 50 mg/min). Following its infusion, fosphenytoin is metabolized rapidly to the active drug, phenytoin. Conversion half-life is 8 to 15 min and independent of plasma phenytoin or fosphenytoin concentrations *(59)*. Despite this conversion delay, fosphenytoin infusion still results in more rapid attainment of therapeutic plasma concentrations (2.7 min for fosphenytoin vs 6.1 min for phenytoin, $p < 0.01$) *(60)*. This has been attributed to the faster infusion rate and to fosphenytoin's displacement of phenytoin from protein binding sites, resulting in higher free phenytoin levels in the presence of fosphenytoin *(58)* (*see* Fig. 4).
2. Fosphenytoin is water-soluble and stored in a buffered solution (pH 8.6 to 9.0), as opposed to phenytoin, which is formulated with 40% propylene glycol and 10% ethanol (pH 12.0). Therefore, fosphenytoin causes less local irritability at the site of injection and is less likely to cause tissue necrosis if extravasated. Because of its caustic characteristics, phenytoin should be delivered through central iv lines, while fosphenytoin can be administered peripherally.
3. Fosphenytoin, unlike phenytoin, is compatible with all iv solutions *(59)*, so separate intravenous lines are not required for medications administered simultaneously.
4. Fosphenytoin, unlike phenytoin, can be delivered intramuscularly with little risk of local abscess formation or intramuscular crystallization. Rates of local irritability were the same as with placebo *(61)*. Although therapeutic plasma concentrations of phenytoin (>10 μg/mL) can be established within 30 min after intramuscular dosing of fosphenytoin and the relatively large injection volumes (up to 20 cc) are well-tolerated (mean dose of 855 mg ± 104 mg) *(61)*, iv loading of fosphenytoin is preferred for treatment of SE if there is venous access.

Most of the adverse effects associated with fosphenytoin (dizziness, ataxia, somnolence, and nystagmus) are attributable to phenytoin. The only adverse effect reported more frequently with fosphenytoin is paresthesia or pruritis of the groin, buttocks, or face—reported in up to 30% of awake patients receiving intravenous loading doses *(62)*. This typically resolves within 5 to 10 min after the infusion is completed and has been attributed to the phosphates produced by the hydrolysis of fosphenytoin to phenytoin *(58)*. There have been rare reports of significant hypotension, arrhythmias, or both in elderly patients or those with significant cardiovascular disease who receive large, rapid infusions *(63)*. These effects are likely due to phenytoin, rather than to the relatively short-lived fosphenytoin.

The recommended loading dose of iv fosphenytoin for the treatment of GCSE is 20 PE/kg, at a maximum infusion rate of 150 PE/min. For a 70-kg adult, a full loading dose can be delivered in under 10 min—three times faster than for iv phenytoin. EKG and blood pressure monitoring should be performed during this period and for 20 to 30 min afterward, to take into account the conversion delay from fosphenytoin

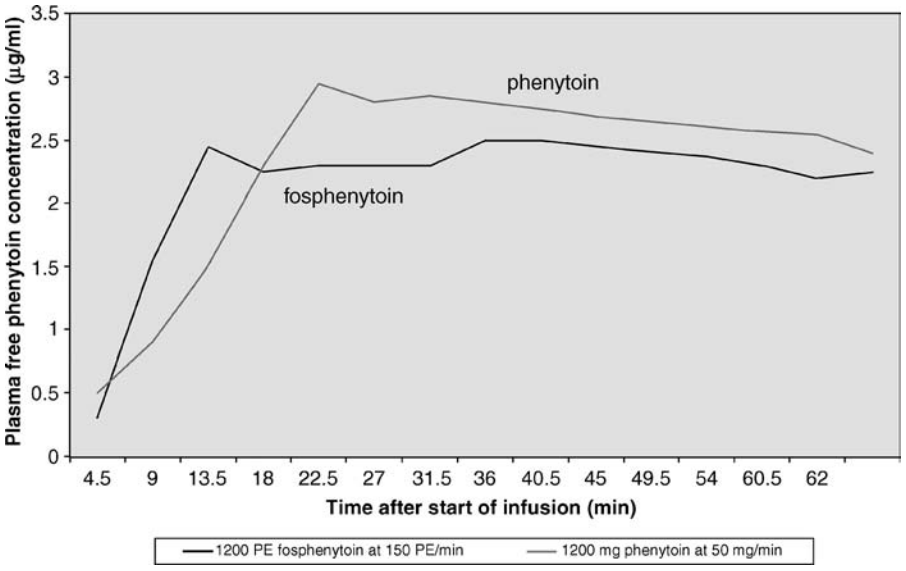


Fig. 4. Therapeutic plasma concentrations of free (unbound) phenytoin (1–2 µg/mL) in healthy adults (n = 12) are obtained earlier after infusion with fosphenytoin than with phenytoin, despite the conversion delay associated with fosphenytoin. Data adapted from ref. *98*.

to phenytoin. If seizures continue after a 20 PE/kg load, an additional 5 to 10 mg/kg can be considered. Serum drug levels of phenytoin are then followed, with a goal of maintaining levels between 15 and 25 µg/mL. Initial phenytoin levels can be checked approx 2 h after administration *(64)*.

Evidence demonstrating fosphenytoin's efficacy in terminating SE is limited to case series. In one series, 59 of 63 adult patients (93%) and all 10 children in GCSE received iv fosphenytoin and became seizure-free; many also received benzodiazepine pretreatment *(58)*. This efficacy is comparable to that of phenytoin *(63)*.

Although fosphenytoin is much more expensive (in 2001, its cost was approx $132.30 for 1500 PE, compared to $12.50 for phenytoin, including tubing and intravenous fluids) *(50)*, iv fosphenytoin is now recommended over phenytoin frequently in the treatment of GCSE, largely based on its comparatively better safety profile and more rapid administration *(14,63)*. Nevertheless, there are no head-to-head comparisons of fosphenytoin with phenytoin or other antiepileptic medications. It is not known whether fosphenytoin's more rapid administration improves efficacy.

3.2.3. Third-Line Agents: Valproate, Phenobarbital

There is no definitive evidence to recommend one agent over another when it comes to third-line treatment. Most clinicians recommend valproate, phenobarbital, continuous midazolam, continuous propofol, or continuous pentobarbital (all given intravenously) *(2)*. The recent trend is for more aggressive treatment if initial doses

of benzodiazepines fail to terminate the SE. This approach is based on a pharmacokinetic rationale. With continuously infused midazolam or propofol, rapid cessation of seizure activity is more likely, but endotracheal intubation is also required, possibly increasing the risk of complications and lengthening hospital stay. (Continuous intravenous midazolam, propofol, and pentobarbital are reviewed in Chapter 14.)

3.2.3.1. iv VALPROATE

The intravenous formulation of valproate (Depacon, Abbott Laboratories, Abbott Park, IL) was introduced in the United States in 1996; it has been available in Europe for more than 15 yr *(65)*. There are no prospective data on its efficacy in treating GCSE; there are case series of patients with refractory GCSE or nonconvulsive SE. Because of the limited data and because it is currently not FDA-approved for use in SE, iv valproate should be considered a third-line agent. It is reasonable to use it in the following scenarios: (1) as an adjunctive agent after proper dosing of benzodiazepines and fosphenytoin; (2) once third-line drugs such as propofol, high-dose midazolam, or barbiturates have failed to control seizures completely; and (3) instead of barbiturates, high-dose midazolam or propofol in patients who have expressed in advance a wish not to receive mechanical ventilatory support *(66)*. Intravenous valproate may also be considered in patients with known allergies to phenytoin or phenobarbital, or who are known to respond well to this drug.

Among its many attractive properties, iv valproate is water-soluble, allowing delivery at a more physiologic pH and along with other medications *(66–68)*. It causes minimal sedation, respiratory depression, or hypotension *(66,68,69)*. It can also be delivered rapidly, with boluses of up to 28 mg/kg infused in under 10 min, without significant side effects *(69)*.

A total of 71 patients (49 adults, 22 children) have received iv valproate for the treatment of GCSE in published case reports *(66–68,70–73)*. Sixty-three (41 adults, 22 children) received iv valproate as either second- or third-line treatment. In 59% of these refractory GCSE cases, it terminated seizure activity without significant side effects. In the eight adults who received iv valproate as initial treatment, seven had seizure activity controlled within 20 min *(70)*. The only significant adverse effect, to our knowledge, was hypotension in a critically ill patient receiving iv diltiazem simultaneously for hypertension; the hypotension resolved as soon as diltiazem was halted *(68)*.

The recommended loading dose of iv valproate for the treatment of GCSE is based on empiric evidence. Currently, it is approved only for boluses of up to 20 mg/kg, but its efficacy in SE may depend on the loading dose and speed of delivery *(65)*. Children receiving boluses of 30 to 40 mg/kg were more likely to respond immediately than those receiving 20 to 30 mg/kg *(66)*. The package insert does not recommend infusion rates greater than 20 mg/min, but data from adults with epilepsy (who were not having seizures at the time) suggest that iv valproate can be given at 5 to 6 mg/kg/min without adverse effects *(69)*.

Hirsch and Claassen recommend that valproic acid serum levels be maintained at 75 to 140 mg/L *(14)*. The upper limit is higher than therapeutic levels usually

recommended for oral valproic acid (50–100 mg/L) *(70)*. This is based on the finding that children who responded immediately to iv valproate had higher blood concentrations (mean 121 ± 9 mg/L; range 103–135) compared to those with a delayed response (93 ± 7mg/L, range 85–102, $p < 0.0001$) *(66)*. In rat models, peak serum levels of 270 mg/L or greater were necessary to control secondarily generalized SE *(74)*. Whether this concentration is safe in humans has not been tested. Serum levels should be monitored frequently, especially when other highly protein-bound medications (such as phenytoin) are administered.

3.2.3.2. iv Phenobarbital

Intravenous phenobarbital has been used in the treatment of SE for many years and is still used commonly in newborns, infants, and children *(1)*. One study compared phenobarbital to diazepam plus phenytoin for the treatment of GCSE *(47)*. Thirty-six adults were randomized to receive either diazepam (up to 20 mg iv) and phenytoin (18 mg/kg iv) or phenobarbital alone (10–20 mg/kg) *(47)*. Primary outcome measures included cumulative convulsion time, defined as the duration of the seizure, and response latency—the time from initiation of treatment to seizure termination. Phenobarbital was slightly more efficacious than diazepam/phenytoin in cumulative convulsion time ($p < 0.06$) and in response latency ($p < 0.10$). The median response latency for phenobarbital was 5.5 min. The mean phenobarbital serum level was 18.3 mg/L (range 15–27 mg/L), generally considered a low level now. Seizures terminated by phenobarbital did so at low serum levels. This study did not have the power to evaluate differences in adverse effects.

Since then, however, phenobarbital has fallen out of favor as an initial agent and is usually used only after lorazepam and phenytoin have failed to terminate seizures *(2)*. Some epileptologists advocate that in cases of refractory SE, it may be more effective to bypass phenobarbital altogether and turn to treatments with a more rapid effect–high-dose benzodiazepines or iv propofol *(2)*. Phenobarbital is much less lipid-soluble than benzodiazepines and therefore has a slower onset of action *(48)*. In animal models, maximal brain concentrations of phenobarbital are achieved 3 min after infusion *(46,54)*, while diazepam reaches maximal brain concentrations within 1 min *(46)*. Furthermore, in doses necessary for the treatment of GCSE, phenobarbital is associated with significant respiratory depression and sedation, often requiring intubation *(1)*. Therefore, there appears to be no advantage to using phenobarbital before continuous iv midazolam or propofol, and possibly many disadvantages. The usual loading dose of phenobarbital is 15 to 20 mg/kg at a maximum rate of 75 to 100 mg/min *(1,14)*. Serum levels should be maintained between 30 and 45 μg/mL *(14)*.

4. OTHER TREATMENTS

Once status epilepticus is refractory to conventional treatment, investigators have turned to a variety of less commonly used treatments, including electroconvulsive therapy *(75)* and surgery *(76,77)*. Experience with these treatments is extremely limited. They should be considered experimental and reserved for only the most refractory situations, when all other treatment options have been exhausted.

Various anesthetic agents have also been reported to terminate refractory SE. Paraldehyde, a hypnotic, can be administered intravenously, intramuscularly, or rectally. There are early reports of its efficacy in treating prolonged convulsions in adults *(78–80)*. A more recent case series demonstrated that multiple doses of iv or rectally administered paraldehyde controlled 38% (6 of 16) of refractory seizures in children *(81)*. Still, paraldehyde is not easy to administer and has been associated with severe adverse effects. It may soften or dissolve polyvinyl iv tubing and may break down spontaneously when exposed to light or air *(82)*. There are reports of several deaths linked to paraldehyde, due to pulmonary edema *(81)*, right heart failure, or pulmonary emboli *(82)*. Paraldehyde can also be irritative to rectal mucosa or cause sterile absesses when administered intramuscularly *(82)*.

Continuous infusions of thiopental, an ultrashort-acting barbiturate, have been used occasionally for refractory SE. In one recent case series, high-dose thiopental was administered to produce burst-suppression activity on EEG; it controlled SE in all 10 patients *(83)*, but nine patients developed clinically evident infections requiring antibiotics, and recovery from this pharmacologically induced coma was prolonged *(83)*. On average, the length of stay in the intensive care unit was 10 d, even though the SE lasted less than 24 h *(83)*. Although clinicians have not noted any difference in efficacy between thiopental and pentobarbital, most prefer pentobarbital because of more extensive experience with it and possibly less cardiac toxicity *(84)*.

Intravenous ketamine, a noncompetitive NMDA antagonist, has potential anticonvulsant and neuroprotective effects. It prevents spatial and associative learning impairment after lidocaine/pilocarpine-induced SE in rats *(85–87)*. In another rat study, ketamine prevented neuronal damage after SE, whether or not electrographic seizure activity was stopped *(88)*. Ketamine's anticonvulsant efficacy may be time-dependent; it was ineffective at terminating seizures if given early in SE (<15 min after onset) but became more effective if administered 60 min after onset *(89)*. These findings have been replicated in animal studies with another noncompetitive NMDA antagonist, MK-801 *(90)*. Williamson and Lothman have speculated that the NMDA receptor-channel complex may have to be activated by seizures for such noncompetitive antagonists to assert their greatest anticonvulsant effect *(90)*. Extrapolating from limited data, some have suggested that ketamine be used as an adjunctive agent in the clinical treatment of SE *(85)*. To date, its use in humans has been limited to case reports *(91,92)*.

The inhalational agent isoflurane was used in one case of epilepsia partialis continua with secondarily generalized SE. It provided adequate seizure control, allowing the patient to be extubated *(93)*. Intravenous lidocaine was used successfully in two patients with refractory SE, and these results were confirmed by EEG monitoring *(94)*.

These agents, however, are not without their own risks. Inhaled anesthetics cause significant hypotension, often requiring vasopressors, while isoflurane has caused increased intracranial pressure *(93)*. Lidocaine at high doses can be proconvulsant *(95)*.

5. CONCLUSIONS

Generalized convulsive status epilepticus is a neurologic emergency, requiring immediate evaluation and rapid treatment. There is evidence to suggest that the earlier the treatment, the more likely the seizure can be terminated. As a result, out-of-hospital treatments have been developed and evaluated. Clinicians should encourage and train caregivers and family to use rectal diazepam or buccal or intranasal midazolam for prolonged or recurrent seizures. Widespread use of these agents early in SE may reduce morbidity and mortality substantially.

In-hospital management of GCSE is based on both experimental and empiric data. Head-to-head comparisons among the most commonly used antiepileptic medications suggest that iv lorazepam is the most effective initial treatment for GCSE, although diazepam is a reasonable alternative. Common practice has been the administration of intravenous fosphenytoin if repeated doses of lorazepam fail. Many practitioners administer intravenous fosphenytoin concurrently with intravenous lorazepam in order to attain therapeutic levels of phenytoin as soon as possible should lorazepam alone fail to control seizures completely. Further research is needed to determine if these practices are warranted. Recently, the trend has been toward beginning aggressive treatment (usually continuous iv benzodiazepines) early in the course of SE. Whether this will result in improved outcome also remains to be shown.

Continuous EEG monitoring is rapidly becoming an indispensable tool in the management of SE. Yet on many levels, how this information should be used is still a matter of debate. How long should patients be maintained in burst suppression before sedating agents can be lowered? Do patients benefit from treatment when there are particular EEG findings or patterns? Controlled clinical studies will be needed to answer these questions.

As understanding of the pathophysiology of SE improves, the management should become more effective. In the future, there may be medications that will not only terminate seizures but also provide neuroprotection and prevent epileptogenesis. This is another area of active investigation. At present, however, no such agents are available, and the best care remains that which terminates the seizure most quickly.

ACKNOWLEDGMENT

The authors thank Dr. Lawrence J. Hirsch for his help and guidance in the preparation of this chapter.

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14
Treatment of Refractory Status Epilepticus

Teresa L. Smith and Thomas P. Bleck

Refractory status epilepticus (RSE) is typically defined as seizure activity lasting more than 1 h that has not been terminated by first- or second-line treatment *(1)*. Based on the results of a randomized controlled trial, lorazepam is commonly accepted as a first-line treatment agent for status epilepticus *(2)*. Phenytoin (or fosphenytoin) is frequently used next, but the likelihood of successful treatment with traditional anticonvulsants is low after failure of the first agent *(3)*. Selection of the third and fourth agents is a matter of controversy, and not the subject of any randomized trials.

There are further problems in the study of RSE treatment. Estimates of its incidence in the United States vary markedly, from 6000 to 159,000 cases per year *(4,5)*. Signs of persistent seizures can be very subtle in patients treated for convulsive SE, so RSE may be difficult to detect, further clouding incidence studies. Also, there is significant heterogeneity among patients with RSE, and outcome is strongly associated with etiology, so different causes of RSE must be considered when comparing treatments *(6)*.

1. PATHOPHYSIOLOGY

The success of anticonvulsants in stopping seizures depends in part on the timing of drug delivery *(7,8)*. When status epilepticus is not controlled early, it is more likely to become intractable *(9)*. After one traditional anticonvulsant has failed, the second traditional agent will succeed in only 7% of cases, and the third in only 2.3% *(3)*.

The pathophysiology of RSE development and propagation is poorly understood. One recent theory involves drug transporter proteins which are part of the ATP-binding cassette (ABC) protein superfamily. RSE can lead to upregulation of ABCB1 and ABCC1, perhaps leading to drug resistance *(10)*. In an animal model, traditional agents such as diazepam, phenobarbital, and phenytoin lose their effectiveness when administration is delayed *(11)*. This suggests an alteration in the function or structure of gamma amino butyric acid (GABA) receptors during (SE). There are several possible mechanisms by which this could occur, including phosphorylation of the receptor or change in the receptor's subunit constituents *(12)*.

From: *Current Clinical Neurology: Status Epilepticus: A Clinical Perspective*
Edited by: F. W. Drislane © Humana Press Inc., Totowa, NJ

Early in the course of SE, persistent seizures may derive from a deficiency of GABA inhibition while later, the pathophysiology may shift to excessive excitatory activity mediated by the NMDA receptor *(13)*. Activation of NMDA receptors may lead to increases in intracellular calcium, which in turn activate kinases, phosphatases, proteases, and other second-messenger systems. These agents could lead to diminished responsiveness to inhibitory neurotransmission. In support of this theory is evidence that the resistance to benzodiazepines in delayed SE treatment may be mediated by the NMDA receptor. In the pilocarpine model of SE in rats, seizures become progressively more resistant to diazepam treatment the longer the delay in therapy *(14)*. Treatment with the NMDA receptor antagonist MK-801 prior to seizure induction, or even 15 or 60 min afterward, can convert diazepam-resistant SE to diazepam-sensitive SE; in this model, the MK-801 did not appear to have innate anticonvulsant activity *(14)*.

2. EPIDEMIOLOGY

RSE represents approx 30% of SE cases *(15)*. In one review of 28 studies describing 193 patients, 60% were female *(16)*. Most were between 28 and 68 yr of age. Eighty-two percent had generalized convulsive status epilepticus at the onset of seizures, and 18% had nonconvulsive SE. The most common primary causes were stroke or tumor in 20%, prior epilepsy in another 20%, toxic-metabolic encephalopathies and CNS infections in 19% each, hypoxic-ischemic injury in 12%, and traumatic brain injury in 5%. Mortality rates were in the 30 to 50% range, with lower rates in those whose RSE was related to underlying epilepsy. Age, higher APACHE-2 scores (a marker of overall medical illness severity), and longer duration of seizures were associated with higher mortality. In this review, greater EEG background suppression, rather than seizure suppression, was associated with a lower frequency of breakthrough seizures but a higher incidence of hypotension *(16)*. Interpretation of this finding is complicated because pentobarbital was used more often when EEG suppression was the goal, and other agents when seizure cessation was the goal. Thus, the EEG goal could be a surrogate for the use of a specific drug.

Individual case fatality rates of SE do not appear to be changing, but its incidence has been rising *(17)*. This may be due to improved detection of nonconvulsive SE and to an increased incidence of myoclonic SE related to anoxic injury after the implementation of improved cardiopulmonary resuscitation techniques in the 1960s. Also, SE mortality is related to age, and the elderly population is growing, while case fatality rates in younger patients are likely improving, leaving the overall mortality rate unchanged *(17)*. Also, compared to convulsive SE, NCSE is more difficult to control *(2)*, and it appears to be associated with the development of RSE *(15)*. "Subtle" SE (evidence of SE on the EEG, but without convulsive movements other than blinking or small jerking movements) tends to occur in patients who are older, more ill medically, and have a lower frequency of underlying epilepsy than those with overt SE *(2)*. All these factors make it difficult to compare mortality rates over the decades.

Mortality rates are higher in those with a longer duration of seizures. When duration is examined as a dichotomous outcome, 30–59 min vs ≥60 min, 1-mo mortality rates were 2.7% and 32%, respectively *(18)*. RSE is associated with a higher morbidity and longer hospital length of stay than nonrefractory SE *(15)*. Despite wide ranges in outcome, prolonged treatment for RSE (up to 53 d in one case *[19]*) can result in a good outcome.

3. EFFECTS OF PROLONGED STATUS EPILEPTICUS

There are many physiologic complications of RSE. Early in SE there are signs of sympathetic overdrive but later, as seizures continue, hypotension, bradycardia, and hypoxemia may develop. Metabolic derangements are common and include hypoglycemia, acidosis, hyperkalemia, and high levels of creatine kinase, related to myoglobinuria and acute renal failure. Cerebrovascular autoregulatory dysfunction may lead to cerebral edema.

Continued seizures can lead to cerebral damage even with adequate oxygenation and muscle paralysis. In humans, Sommer's sector and the CA3 region of the hippocampus show lower neuronal densities in patients with a history of SE than in matched controls *(20)*. Although there are methodologic difficulties in studying any cognitive dysfunction that might result from prolonged seizures, it appears that intellectual impairment may result from seizures lasting more than 30 min *(21)*. Some patients appear to have greater susceptibility to cognitive dysfunction than others *(21)*.

4. TREATMENT

4.1. Barbiturates

Barbiturates are used commonly for the treatment of RSE (*see* Chapter 9) despite the high rates of associated hypotension *(6)*. The anesthetic barbiturates have an advantage over phenobarbital in that they are direct GABA-mimetic agents *(22)*. Although there are no data to support superior efficacy of one barbiturate over another for the treatment of RSE, pentobarbital is used often. It has a shorter half-life than phenobarbital and is less cardiotoxic than thiopental *(23)*. Of 40 patients with RSE treated with pentobarbital in one series, 39 achieved clinical and electrographic control of seizures *(6)*. Twenty-six were treated successfully, nine had relapses, and five died during initial treatment. Although pentobarbital treatment was delayed for more than 12 h after seizure onset in 21 patients, this was not associated with a worsened outcome. Despite the long half-life, tapering pentobarbital may be associated with fewer relapses than abrupt withdrawal *(6)*.

Although the EEG goal of treatment is unclear (a "flat" EEG vs burst suppression vs cessation of seizures), those treated with pentobarbital with flat EEGs tended to have slightly better outcomes than those with burst suppression *(24)*. Interestingly, the occurrence of hypotension was not associated with the dose of pentobarbital or the degree of EEG suppression *(24)*.

Despite monitoring of serum pentobarbital concentrations, a specific level at which seizures cease has not been identified *(23)*. Pentobarbital levels can be

detected up to 8 d following its cessation *(25)*, and patients can develop reversible side effects including diffuse weakness, confusion, and ataxia after recovering consciousness *(23)*. One protocol recommended a loading dose of 15 mg/kg over 1 h followed by an infusion of 0.5 to 2.0 mg/kg/h *(26)*.

Prognosis was assessed in 17 patients with RSE treated with pentobarbital for 13.5 h to 29 d *(27)*. Slightly more than half died from what were thought to be complications of the underlying disorder. Of the eight who survived, only two had a poor outcome, with a severe decline in neurologic status. The other six had minimal or no change from neurologic baseline at hospital discharge.

In a series of 10 patients with RSE treated with thiopental, all had successful seizure control *(28)*. Four required pressors, and all required intravenous fluids to maintain blood pressure. The protocol included 5 mg/kg thiopental at first, and 1 to 2 mg/kg boluses until burst suppression was achieved, followed by an infusion of 5 mg/kg/h. A wide range of doses was required to achieve burst suppression. Intensive-care unit (ICU) care was thought to have been prolonged by sedation from the thiopental. In animals, thiopental appears to be more cardiotoxic than pentobarbital when given in doses causing comparable EEG effects *(29)*.

Some advocate the addition of phenobarbital for those who remain refractory to treatment *(19)*. There appears to be no ceiling effect to its anticonvulsant activity, so progressively increasing doses can be used. Despite high doses, tolerance to the respiratory-depressant action and sedative properties develops. Some authors caution that very high doses of phenobarbital may be accompanied by a higher risk of toxicity from propylene glycol contained in the phenobarbital vehicle *(30)*.

4.2. Midazolam

Midazolam is a short-acting benzodiazepine that has gained popularity in the treatment of status epilepticus. Its mode of action is by enhancing GABAergic transmission through the $GABA_A$ receptor. There are case series of its use in RSE. In one series of seven patients previously treated with lorazepam, diazepam, and phenytoin, all had cessation of clinical and electrographic seizures after initiation of midazolam; only one developed hypotension *(31)*. Due to its short effects, midazolam facilitates decreased time in the ICU after its discontinuation. Nevertheless, even in those without renal or hepatic dysfunction, it may have a prolonged effect after sustained infusion, possibly due to its accumulation in adipose tissue *(32)*.

The effective dose of midazolam required to treat RSE varies widely. Typically, a bolus of 0.2 mg/kg over 5 min is followed by an infusion of 0.05 to 0.4 mg/kg/h *(1)*. In a small retrospective analysis, midazolam and propofol had similarly high rates of seizure control, but those treated with midazolam had a lower mortality rate (although not statistically significant) *(33)*.

In a retrospective analysis of 33 episodes of RSE (17 convulsive and 16 nonconvulsive at onset), continuous midazolam infusions led to seizure cessation within 1 h of treatment initiation in 82%, without recurrence between 1 and 6 h *(1)*. Of the 33 episodes, 18% could not be controlled eventually with the midazolam infusion.

4.3. Propofol

Propofol is an intravenous general anesthetic. As with benzodiazepines and barbiturates, its mode of action is by enhancing GABAergic transmission through the $GABA_A$ receptor. In a series comparing propofol and barbiturates (primarily pentobarbital), control of seizures was attained in five of eight propofol-treated patients and 9 of 11 treatments with the barbiturate (barbiturates were used in case of propofol failure) *(34)*. Seven of eight propofol-treated patients and four of eleven barbiturate-treated patients died. The mean time to seizure control in patients who responded to propofol was 2.6 min, compared to 123 min with barbiturates. Monitoring of propofol levels demonstrated rapid clearance even after a prolonged infusion. Correspondingly, resumption of seizures was more common when propofol was stopped abruptly than when it was discontinued slowly. The authors recommend a taper of 5% per hour of the maintenance infusion *(34)*. The protocol included a bolus of 1 to 2 mg/kg followed by a maintenance of 1 to 15 mg/kg/h. This yielded plasma levels greater than those required for sedation but lower than those needed for maintenance of general anesthesia.

Propofol has the advantage of a rapid onset effect and short-lived sedation, but it does cause cardiac suppression or hypotension and can lead to metabolic acidosis. It is formulated in a lipid solution that should be factored into the patient's daily nutritional requirements. The safety of propofol for the treatment of RSE in children is in question because it has been associated with hypoxia and rhabdomyolysis *(35)*.

4.4. Anesthetic Agents

The use of inhaled isoflurane for RSE was demonstrated in a series of nine patients *(36)*. Each had been treated unsuccessfully with benzodiazepines, phenytoin, and phenobarbital before initiation of general anesthesia. There was at least an attenuation of seizure activity in all patients. A burst-suppression pattern was the most common EEG rhythm attained. All patients required intravenous fluids or pressors to maintain an adequate mean arterial pressure. Six of nine patients died. Two had multiorgan failure. Prolonged use of isoflurane can be associated with the release of fluoride ions, which did not reach nephrotoxic levels in this series *(36)*.

There may be less rise in cerebral blood flow and associated increased intracranial pressure with isoflurane than with halothane. Isoflurane also carries a lower risk of hepatotoxicity, as it undergoes less metabolism *(37)*. In an animal model, however, halothane provided neuroprotection from hippocampal damage related to electrode stimulation *(38)*. It is unknown whether this is an effect of all drugs in this class or whether this translates into a specific and meaningful beneficial effect of halothane in humans.

Desflurane is pharmacodynamically and pharmacokinetically similar to isoflurane but is probably even more resistant to biotransformation and is a reasonable alternative to isoflurane *(39)*. All the volatile anesthetics are inconvenient to administer and require a gas retrieval system.

A series of eight patients demonstrates the possible usefulness of etomidate in treating RSE *(40)*. Each patient had been convulsing actively for at least 6 h despite multiple anticonvulsants. Etomidate terminated seizures in all patients. Blood pressure lowering was minimal with initiation of treatment; five patients had episodes of hypotension during maintenance infusions. Two of the eight patients died, four returned to their premorbid conditions, and two were debilitated at 6 mo. Steroid replacement must be used with etomidate because its imidazole group reversibly inhibits cortisol synthesis *(40)*.

Many neurologists are not familiar with etomidate. For induction of anesthesia, 0.2 to 0.4 mg/kg can be given *(41)*. It has a β-phase half-life of 2.9 h, similar to that of ketamine. The mean initial infusion rate in the series above was 25 μg/kg/min, but tachyphylaxis was not uncommon *(40)*.

Ketamine is metabolized by the cytochrome P450 system to its active metabolite, norketamine. Unlike most general anesthetics, ketamine does not have a significant effect on the $GABA_A$ receptor. Instead, it inhibits the NMDA receptor by binding to its phencyclidine site *(41)*, making it a good candidate when GABAergic drugs have failed. Another important distinction is that it is associated with a rise in blood pressure, heart rate, and cardiac output, which can be useful effects for patients in RSE.

In an animal model, ketamine was effective in controlling seizures of long duration, but with less success if administered early in the SE course, supporting the theory that early SE is predominantly a disorder of lack of inhibition and later becomes a disorder of overexcitation *(13)*. This suggests trials of ketamine in benzodiazepine-resistant RSE.

In one case report, ketamine controlled seizures in a 13-yr-old who was unable to be weaned from pentobarbital coma despite trials of lorazepam, valproate, lidocaine, and propofol *(42)*. In a retrospectively collected series of seven patients with RSE, two had seizure cessation after a loading dose of ketamine and another two gained seizure control with an infusion *(43)*. In this series, loading doses were 0.9 to 3.0 mg/kg and infusions, 0.3 to 5.8 mg/kg/h.

4.5. Lidocaine

Higher doses of lidocaine may be associated with seizures, but lower-dose infusions can be used to treat RSE. A bolus of 1 mg/kg followed by an infusion of 1 mg/min controlled RSE in one case report *(44)*. Three of four patients in another series had immediate cessation of seizures after a single bolus of 100 mg of intravenous lidocaine *(45)*. Boluses of 1.5 to 2.0 mg/kg followed by infusions of 3 to 4 mg/kg/h can be repeated if there are relapses *(46)*.

The mechanism of action of lidocaine may be related to membrane stabilization and a limitation of neuronal recruitment due to lower extracellular potassium *(45)*. One advantage to the use of lidocaine for RSE is that it is not associated with the same risk of hypotension and sedation as many of the other drugs. There is evidence from animal models, however, that concentrations of brain lidocaine increase in the setting of seizures, raising concern for lidocaine toxicity, including the possibility of exacerbating seizures *(47)*. Additionally, lidocaine appears to increase seizures and

mortality associated with cocaine in animals *(48)*. For patients in whom cocaine use cannot be ruled out, it is reasonable to select an alternative agent for treating RSE.

4.6. Valproic Acid

In a series of 41 children (neonates up to 16 yr old) who had SE refractory to diazepam, phenytoin, and phenobarbital, intravenous valproate stopped clinical and electrographic seizures in 78% *(49)*. This success included eight of nine patients with partial onset tonic-clonic SE, 9 of 10 with generalized tonic-clonic SE, 4 of 5 with absence SE, and 4 of 5 with complex partial SE. The treatment regimen consisted of a 20 to 40 mg/kg loading dose given over 1 to 5 min, followed by an infusion of 5 mg/kg/h. Assessment of valproate levels 4 to 6 min after the initial dose showed that those with higher initial levels were more likely to respond. The most successful loading doses were between 30 and 40 mg/kg (compared to both higher and lower doses). There were no significant abnormalities in vital signs or routine laboratory testing, suggesting that intravenous valproate is well-tolerated and free of the resultant hypotension and cardiac toxicity of many other treatments for RSE.

In an open label trial of intravenous valproate in 21 patients with epilepsy who were not actively seizing, loading doses of 25 mg/kg were well-tolerated at rates up to 300 mg/min and yielded levels of 100 to 200 μg/mL (100 to 150 μg/mL in most) 20 min after infusion *(50)*. No electrocardiogram or blood pressure changes were found. All patients denied CNS side effects, and mental status changes were not observed by the examiners. Injection site reactions can occur but may be related to the concentration. When administered for RSE, intravenous valproate appears to be safe. It aborted seizures in one of four patients after a load of 20 mg/kg over 5 to 10 min, resulting in a mean level of 75 μg/mL *(51)*.

Limited efficacy data are available for parenterally administered valproate. In a retrospective review of 18 children treated with parenteral valproate, all had resolution of SE with resumption of normal mental state within 1 h of treatment *(52)*. Efficacy data for valproate are limited for the treatment of RSE, but a drug that allows for quick recovery of wakefulness appears valuable.

4.7. Topiramate

Due to its multiple modes of action, topiramate is thought to be a good candidate for the treatment of drug-resistant RSE. It attenuates experimental SE-induced hippocampal damage in animal models *(53)*. Unfortunately, there is no parenteral preparation, so topiramate must be crushed, mixed with water, and administered through an orogastric or nasogastric tube. Although outpatient starting doses of topiramate are typically very low in an attempt to avoid side effects, up to 1600 mg has been given in less than a day for RSE *(54)*. In a series of six patients, topiramate treated SE successfully in all cases, with doses of 300 to 1600 mg *(54)*. Lethargy was the only side effect noted.

4.8. Vagus Nerve Stimulation

The possible role of vagus nerve stimulation (VNS) in treating RSE was investigated in three patients with histories of partial seizures who developed RSE due to

anticonvulsant withdrawal and failed lorazepam, phenytoin, phenobarbital, and valproate treatment *(55)*. The duration of RSE prior to VNS implantation was 1 to 5 wk. Each patient had the VNS device escalated to the maximum current with rapid cycling (3 mA current, 30 Hz stimulation, with pulse width 500 μs, with on time 60 s and off time 60 s) with cessation of seizures 3 to 5 d after implantation. This suggests a role for compassionate use of VNS in carefully selected patients.

4.9. Neurosurgical Treatment

Although there have been no trials investigating the role of epileptic focus resection in the treatment of RSE, there have been reports of its success. When clinical, electrographic, structural, and functional neuroimaging evidence are in concordance, the seizure focus can be identified and possibly resected *(56)*. The role of surgical intervention in the treatment of RSE has not been defined yet.

5. CONCLUSION

Refractory status epilepticus is an important neurologic emergency with a substantial mortality rate. There are numerous agents that can be used for its treatment, but clinical trial data on their use are lacking. Success rates of traditional anticonvulsants fall significantly after the failure of the first agent, and continuous drug infusions are often necessary to control persistent seizures. Because SE becomes more intractable as it continues, and because it is associated with significant morbidity and mortality, aggressive treatment should be launched early, with continuous EEG guidance. RSE may become resistant to benzodiazepines and other traditional agents, so it is important to be familiar with alternative drug choices. Future directions for research may include hypothermia and novel therapies for altering drug transporter proteins *(57,58)*.

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15

Treatment of Nonconvulsive Status Epilepticus

Frank W. Drislane

1. RATIONALE FOR TREATMENT

Generalized convulsive status epilepticus (GCSE) usually has stereotyped manifestations and is easy to recognize. It is clearly a medical and neurologic emergency, and many protocols or regimens have been advanced for its treatment. Many neurologists believe strongly that having a treatment protocol, or at least a plan in mind, facilitates treatment and promotes better results. This is not so straightforward with nonconvulsive status epilepticus (NCSE).

How urgently and aggressively should NCSE be treated? Clinical outcome and pathologic studies are not conclusive. Experimental pathologic studies show lasting neuronal injury from GCSE, but clinical studies show little evidence of permanent neurologic injury from most episodes of NCSE. Nevertheless, it would be unwise to ignore the prolonged memory dysfunction in several well-reported cases, and NCSE has some similarities to convulsive SE (*see* Chapter 12). A minority of episodes of NCSE might lead to significant deficits. From case reports and by analogy to GCSE, the more prolonged cases may be worse *(1)*, and NCSE may last for days without proper diagnosis. Episodes associated with focal lesions such as strokes may entail two processes, with a greater chance of lasting harm *(2)*. Concomitant systemic factors such as infection, metabolic disturbances, hypotension, and medications might increase the likelihood of damage in a synergistic fashion *(3)*. Finally, by extrapolation from experimental studies, episodes of NCSE with more rapid (and presumably excitatory) epileptiform discharges may be more worrisome *(4)*. Whatever the long-term risks, there is a clinical need to treat: Patients in NCSE have abnormal mental status or other deficits (by definition), and treatment can return them to normal functioning.

NCSE comes in a remarkable variety of presentations (*see* Chapter 10). It occurs as manifestations of many different epilepsy syndromes, ranging from the noninjurious and readily treatable, typical primary generalized absence SE to the refractory NCSE following generalized convulsions or occurring in very ill, comatose patients. While there are many published treatment protocols for GCSE, all reports of the treatment of the different NCSE syndromes are retrospective cases or series.

From: *Current Clinical Neurology: Status Epilepticus: A Clinical Perspective*
Edited by: F. W. Drislane © Humana Press Inc., Totowa, NJ

Whatever the syndrome or type, NCSE often responds well to initial benzodiazepine treatment, but there are many exceptions. Valproic acid has also been a popular treatment, in part because of its use in primary generalized epilepsies but also because of its broad-spectrum applicability and availability in intravenous form. Usually, underlying medical and neurologic precipitants for NCSE must be found and treated if the SE is to be brought under control promptly. Infections must be diagnosed and treated simultaneously. Patients who have NCSE because of low antiepileptic drug (AED) levels are best treated with increases in those drug levels, although the SE may need to be interrupted first by intravenous benzodiazepines. Patients without earlier epilepsy may not require long-term AED treatment; those with underlying structural lesions may require prolonged treatment.

Because of the lack of obvious clinical imperative in treating some cases of NCSE, the physician must weigh the risks of the illness against the possible complications of treatment. Treatment of NCSE is often easier than diagnosis, but when initial interventions are unsuccessful subsequent treatment can become far more complicated and difficult. Different forms of NCSE warrant different treatments. Kaplan points out that "the etiologic diversity underlying the onset of NCSE mandates an individualized approach" *(5)*.

2. ABSENCE SE

Early reports of absence SE (ASE) tended to describe patients with a history of typical primary generalized epilepsy, including absence seizures. Oral barbiturates, ethosuximide *(6)*, and intravenous phenytoin were effective treatments *(7)*. Inhalation of carbon dioxide interrupted discharges in one patient, but intravenous benzodiazepines and barbiturates were generally more effective *(6)*. Later reports included less classic or atypical ASE, often with a delayed response.

Straightforward cases of idiopathic ASE may be terminated by intravenous benzodiazepines relatively quickly *(8)*. Shorvon recommends intravenous diazepam 0.2 to 0.3 mg/kg or lorazepam 0.07 mg/kg as initial treatment for ASE *(9)*. This may be repeated if necessary or followed by intravenous phenytoin or valproate. Acutely, intravenous valproate can also be helpful *(10)*. This does not mean that other medications would be ineffective, especially given the overlap syndromes and the possibility that many episodes of supposed 'absence' SE are actually secondarily generalized, focal-onset seizure syndromes.

Older patients with *de novo* absence SE often have precipitants such as benzodiazepine withdrawal (8 of 11 cases in one series) *(11)*. This usually responds to brief courses of benzodiazepines, although barbiturates may also be helpful. Nine of eleven patients with *de novo* ASE had an immediate cessation of EEG abnormalities when treated, and the other two cleared after 48 and 72 h *(11)*.

Paradoxical effect: When ASE occurs in the setting of idiopathic primary generalized epilepsy, AEDs that are not appropriate for such epilepsies may actually worsen the seizures or SE. AED precipitation of NCSE may also occur more often in patients with refractory epilepsy. Several AEDs useful for partial and secondarily generalized seizures have been reported to exacerbate primary generalized seizures.

Phenytoin and carbamazepine may be particularly inappropriate treatments in many of the primary generalized epilepsy syndromes, and they may produce a paradoxical effect leading to ASE refractory to benzodiazepines *(12)*. With typical ASE or presumed primary generalized epilepsies, most epileptologists would avoid phenytoin (despite the reports cited above), carbamazepine, and phenobarbital. Benzodiazepines, valproic acid, and other usual treatments for absence epilepsy are preferable.

Recurrence: In idiopathic absence SE, recurrence is the rule in most patients until adequately treated *(13)*. Andermann and Robb reported a patient who had episodes of SE lasting up to 2 d every 2 or 3 wk for the last 25 yr of her life *(6)*. Berkovic and colleagues assessed recurrence in 25 patients with absence SE *(13)*. Those with diagnoses of primary generalized epilepsy had such episodes almost six times a year before treatment with valproic acid but only about once every other year in 4 yr of follow-up on valproate. Indeed, 14 of these 18 had no recurrence at all and three had recurrences only when missing medication. Less typical absence SE patients with underlying lesions did not have as good a response but appeared to benefit from valproate treatment.

Older patients with *de novo* absence SE may not need long-term AEDs, particularly when episodes are precipitated by use of psychotropic medications (such as neuroleptics, tricyclic antidepressants, and lithium) or withdrawal of benzodiazepines *(11)*. Most remain free of ASE recurrence even without chronic AED treatment. Those with earlier idiopathic generalized epilepsies, e.g., childhood absence seizures, may have late-onset ASE after decades of remission. These patients may need more prolonged treatment to prevent recurrences. When longer-term treatment is necessary, valproate has been effective *(13*).

3. COMPLEX PARTIAL STATUS EPILEPTICUS

Some complex partial status epilepticus (CPSE) cases reported by Ballenger and colleagues had continuous seizure activity, and other cases included recurrent discrete episodes without recovery between them *(14)*. CPSE occasionally resolves spontaneously after several hours, i.e., without administration of AEDs *(15)*. If consciousness and ability to swallow are maintained, many cases can be treated with oral anticonvulsants, often using more of the same medications the patients were taking earlier. CPSE may also be interrupted by intravenous benzodiazepines *(9)*. Many investigators recommend treating CPSE in exactly the same way as for GCSE, beginning with benzodiazepines and following with longer-acting medications such as phenytoin *(16)*. Focal onset NCSE is often less responsive to intravenous benzodiazepines than is classic primary generalized absence SE or generalized NCSE.

Many cases of CPSE were interrupted and controlled with traditional intravenous AEDs such as phenytoin, phenobarbital, and diazepam, or oral carbamazepine, but newer drugs were not available at the time of those early case reports *(14,17–19)*. More frequently, intravenous benzodiazepines are used to interrupt the NCSE once it is recognized, but NCSE may recur after initial success in treatment *(20);* many of these patients required additional intravenous phenytoin before responding.

CPSE in nontemporal areas can be more refractory to treatment than CPSE of temporal lobe origin. This could represent a detection bias, with CPSE being harder to diagnose in extratemporal cases; thus, more refractory cases come to medical attention. One patient with occipital origin CPSE required diazepam, phenytoin, and phenobarbital *(21)*.

Similarly, CPSE of frontal origin is often described as difficult to treat *(22)*. While most forms of NCSE respond readily to intravenous benzodiazepine and several other treatments, CPSE of frontal origin may occasionally be quite refractory. Ten patients with frontal-onset CPSE included six with focal lesions, and 8 of 10 did not respond to the initial intravenous benzodiazepine *(22)*. Intravenous phenytoin controlled six of those successfully, and all did well clinically. Another required the addition of carbamazepine. One required 48 h of pentobarbital. The initial diagnosis was typically delayed for 48 h in these patients; once again, more prolonged NCSE is more likely to become refractory to treatment.

Recurrence: CPSE is particularly likely to recur, and patients are less likely to remain off medication (compared with those with ASE). In one series, 17 of 20 patients had recurrences, some up to weekly *(23)*. Finding remarkably good outcomes clinically, this group did not recommend aggressive treatment. Intravenous benzodiazepines were not always successful, and valproic acid did not appear particularly effective in preventing recurrences—in contrast to its great value in ASE. CPSE often occurs in patients with earlier focal lesions and complex partial epilepsy. These patients rarely cease having seizures (and episodes of CPSE recur often) without continuing AED treatment. A variety of standard traditional AEDs may prevent recurrences *(24)*.

4. NONCONVULSIVE STATUS EPILEPTICUS IN GENERAL

Most of the larger clinical series include mixtures of types of NCSE, not further specifying generalized (absence) or focal-onset (complex partial) SE. Most individual patients in these series probably had NCSE secondarily generalized from a focal onset. Though mixed in types of SE, most outcomes were good. Some NCSE ends spontaneously, and others may end if the precipitating cause, such as medication or infection, is removed. Removal of certain antibiotics may be helpful *(25)*. Three of 32 patients with NCSE in one series recovered spontaneously during the initial EEG recording and did not require AEDs *(20)*.

For the rest, benzodiazepines are used nearly uniformly to interrupt NCSE, and they are often successful *(20,26)*. Of 10 patients with generalized NCSE reported by Guberman and colleagues, 2 ended spontaneously, and the other 8 had resolution of the SE within 2 min when given intravenous benzodiazepines *(26)*. For most NCSE, lorazepam may be the drug of choice *(27)*. Patients with earlier epilepsy as the background or cause of NCSE may respond well to increases in their usual AEDs, especially if missed or subtherapeutic medication was the precipitant for this particular episode. If patients are already receiving phenytoin, intravenous fosphenytoin may be beneficial.

In one series, all older patients with ictal confusion as a manifestation of generalized NCSE responded well to intravenous diazepam, followed by oral phenytoin

or phenobarbital *(28)*. Intravenous or rectal benzodiazepines can interrupt NCSE in children, even in such relatively difficult or refractory situations as Lennox-Gastaut syndrome or myoclonic astatic epilepsy and generalized NCSE *(29)*. Some period of sedation may precede improvement. Subsequently, adjustments may need to be made in the baseline AEDs.

One NCSE group had predominantly absence SE (18 of 22 cases), and the majority had earlier epilepsy *(30)*. There were many (usually medical) precipitants. Earlier psychiatric disorders and cerebrovascular disease complicated diagnosis. Most patients appeared confused or moderately unresponsive, but staring and myoclonic jerks were common. Automatisms were less common. Fourteen patients responded rapidly to intravenous benzodiazepines; some required longer treatment with maintenance anticonvulsants.

NCSE with a focal onset, whether or not generalized later, is often harder to control. In one series, 90% of patients with generalized discharges had a good response to diazepam (resolution of EEG discharges) while only 60% with focal discharges did *(31)*. All clinical improvements occurred with doses of 8 mg diazepam or less; 3 mg was the typical dose. Most patients in another series had histories of earlier epilepsy, and most appeared to have seizure activity secondarily generalized from an initial focal onset; the group had mixed types of NCSE *(20)*. Almost all responded immediately to intravenous benzodiazepines, but most had recurrences and needed longer-term treatment.

Of four patients with NCSE and peritoneal dialysis for end-stage renal disease all appeared to recover neurologically with appropriate treatment, although two died of pneumonias shortly thereafter *(32)*. All 10 patients with NCSE attributed to a combination of renal failure and cephalosporins recovered when the antibiotic was withdrawn and after treatment with clonazepam and sometimes other AEDs; 8 of 10 required anywhere from 2 to 7 d for clinical improvement *(25)*.

Paradoxical effect: Infrequently, vigabatrin and tiagabine have been reported to precipitate or worsen generalized NCSE *(33,34)*. Many case reports implicated tiagabine in NCSE exacerbation, but an epidemiologic study suggested that some reported cases were actually drug-induced encephalopathies (not SE) and that actual cases of NCSE were no more common than would be expected in patients with epilepsy *(35)*.

Delayed response: The response to treatment can be delayed in NCSE, especially after generalized convulsions. Fagan and Lee described eight patients with prolonged generalized NCSE following generalized seizures that had appeared to cease *(36)*. All patients responded to increased AEDs, but always after substantial delays. EEG discharges may resolve quickly with intravenous benzodiazepines, but the clinical improvement was delayed anywhere from hours to 2 or 3 d, although all improved eventually. Other patients labeled with absence SE (but possibly secondarily generalized SE) had a gradual recovery with benzodiazepines rather than an immediate response *(37)*.

Dunne and colleagues also found a more gradual recovery with treatment of CPSE than with generalized or absence SE *(30)*. Although intravenous benzodiazepines were successful, improvement tended to take 12 to 48 h after treatment for NCSE, especially in patients who had been in SE for at least 36 h.

Patients who have been in NCSE for longer times may respond even more slowly. Among 23 patients with difficult-to-diagnose NCSE in an emergency room (ER), intravenous benzodiazepines (usually with subsequent phenytoin or longer-acting anticonvulsants) were always successful. The median duration of the clinical deficit before presentation in the ER was 2 d (range 3 h to several weeks), and the time to diagnosis once in the ER was a median of just under 1 d but could be up to 4 d. EEGs on these patients improved quickly, with a median time to EEG improvement of 10 min (and all who improved did so within a day), but the median time to *clinical* improvement was just under a day *(27)*. Especially for patients with long durations of NCSE, it may take at least many hours to improve clinically. An immediate response to medications should not be anticipated.

It is clear from several series that intravenous benzodiazepine treatment can have immediate and dramatic effects on the EEG without leading to a clinical improvement, or one with a delay of up to a few days. Also, the EEG may show a marked resolution of sharp features after benzodiazepine administration without those sharp features actually representing seizures or SE, e.g., the triphasic waves of a metabolic encephalopathy may respond rapidly to benzodiazepines *(38)*. These observations should prompt serious doubts about the value of an immediate response to AEDs (or even more so, its absence) in determining the diagnosis of NCSE.

Recurrence of NCSE: In a series of 32 NCSE patients, many had an immediate and permanent improvement with benzodiazepines, but two thirds had recurrence within hours if benzodiazepines were used alone *(20)*. Guberman and colleagues followed eight patients with generalized NCSE for an average of almost 6 yr, and all but one had several recurrences, one with episodes of NCSE twice a year for more than 20 yr *(26)*. Almost all patients remained on valproic acid or ethosuximide, often with phenytoin or carbamazepine, as well.

Several older patients had recurrences of NCSE when AEDs were discontinued. Tomson and colleagues described 10 adult patients with NCSE *(37)*. Five had CPSE, and the five with generalized EEGs were considered to have "atypical" absence SE. Intravenous benzodiazepines interrupted the SE promptly in all, but eight relapsed within a few hours. These were controlled with repeated benzodiazepines or, in most cases, with the addition of phenytoin. Six required longer-term phenytoin. Thus, all patients had SE other than typical idiopathic generalized ASE and tended to require maintenance AEDs to prevent relapse.

5. PROLONGED NCSE

Because of its subtle presentations, NCSE may have progressed for a long time before diagnosis, especially in the setting of severe medical and neurologic precipitating illnesses (or both). Some episodes of NCSE become prolonged and require additional treatment, but when NCSE continues for many hours or even days, it often responds less well to AEDs.

Many episodes of NCSE are interrupted or even treated completely by intravenous benzodiazepines, but not all treatment is effective immediately, and the clinical response can be slow. Many patients with NCSE have an inadequate initial

response to benzodiazepines *(20,31)*. Single doses may cause a transient improvement but lead to relapses as the effect of the medication wears off. Continuous or maintenance use of benzodiazepines is of possible benefit, but often it is necessary to establish therapeutic levels of longer-acting AEDs.

Increasing the levels of already-utilized AEDs may be useful *(5)*. They may improve the level of consciousness if that diminished consciousness is due to ongoing seizures *(39)*. Maintenance of higher doses and levels of AEDs used in the management of chronic epilepsy, such as phenytoin and phenobarbital, can be helpful over a longer period *(36,39)*. AEDs without an iv formulation may be given enterally (by nasogastric tube or rectally) over days in refractory cases, but enteral carbamazepine and rectal valproic acid may not be so helpful when difficulties with administration or absorption lead to inadequate serum levels *(39)*. Fortunately, valproate can be given intravenously now. Carbamazepine and topiramate are among several AEDs that are not given intravenously. Enteral topiramate doses of up to 1600 mg/d have been used successfully in some cases *(40)*.

In these prolonged, refractory cases of NCSE, intermittent small doses of benzodiazepines may contribute to therapy but are seldom sufficient. Once the NCSE is recognized, some groups recommend starting treatment with intravenous benzodiazepines, followed by intravenous loading doses of fosphenytoin at 20 mg "phenytoin equivalent" per kg *(41)*. If this is unsuccessful, they recommend continuous therapy with intravenous midazolam (with an initial bolus of 0.1 to 0.2 mg/kg over 5 min followed by a maintenance infusion of 0.05 to 0.4 mg/kg/h). Usually, it is impossible to know whether the ongoing seizures have been interrupted without an EEG. Continuous EEG monitoring is almost always appropriate in order to see whether NCSE is continuing or whether control has been attained. Knowing this, one can adjust the continuous infusion dose, add or taper AEDs, or make other changes in treatment plans.

6. REFRACTORY NCSE IN PATIENTS WITH SEVERE MEDICAL AND NEUROLOGIC ILLNESS

Electrographic SE and the NCSE discovered after clinically recognized generalized convulsions or GCSE can be particularly refractory. Subclinical or electrographic SE in patients with severe medical and neurologic illnesses is also very difficult to control. Only a minority of these cases may respond to initial AED treatment *(42)*. Benzodiazepines may control clinical seizures or suppress EEG discharges without leading to a clinical improvement, especially if the depressed mental status is due to an underlying illness *(39)*. In one group of 74 patients discovered to have nontonic-clonic SE (primarily by EEG), nine did not respond to standard AEDs and required pentobarbital treatment *(43)*. The usually poor outcome of these patients is discussed in Chapter 12.

Though it is often reserved for GCSE, extensive, "aggressive" treatment may be warranted in some cases of NCSE. Treatment usually follows the recommendations for treatment of refractory status detailed in Chapter 14. It often includes pentobarbital, propofol, or long-term continuous infusion of benzodiazepines such as midazolam or

lorazepam. It can involve prolonged suppression of seizures, with or without suppression of the EEG, but always with concurrrent EEG data to guide treatment. Some treat to stop clinical seizures, but electrographic seizures must be controlled also. Some aim for a burst-suppression pattern on EEG, but there are no reliable clinical trials to guide this approach. When treatment controls SE, at least electrographically, there are no good data to indicate when such aggressive treatment should be tapered or withdrawn. Traditionally, this has been attempted after 12 to 24 h, but the choice of time is guesswork. Retrospective data with pentobarbital raised the possibility that longer periods of EEG seizure suppression may be helpful *(44)*.

7. COMPLICATIONS OF TREATMENT

Because NCSE can be a manifestation of innumerable different illnesses, its clinical manifestations, origins, and outcomes are remarkably varied. Its treatment does have potential risks and toxicity, including hypotension. Many patients with refractory NCSE and serious medical or neurologic illness are older, and some do not tolerate the hemodynamic (and hypotensive) effects of barbiturates and benzodiazepines. Intravenous valproate may be better tolerated and can be helpful in the control of SE *(45)*. Overtreatment may cause respiratory suppression, and even respiratory failure. NCSE patients with respiratory and infectious problems are much more likely to die, suggesting that medical complications should be looked for and treated, or prevented if at all possible *(3)*. Such complications may explain much of the morbidity and mortality of NCSE, even while NCSE itself is rarely fatal.

In one series, critically ill elderly patients with NCSE were more likely to die when treated with intravenous benzodiazepines than when treatment did not include benzodiazepines *(46)*. Half the patients treated with benzodiazepines had immediate respiratory depression, and many had hypotension. Several developed pneumonias. This raised the possibility that aggressive treatment actually worsened the outcome, but most patients in this series had severe medical and neurologic illnesses—correlated with high mortality in many series. Treatment of NCSE represents a balance between these risks and the clinical need for treatment, with the threat of neuronal damage. Treatment must be tailored to fit the type of SE and clinical urgency *(47)*.

8. CONCLUSIONS

Treatment of NCSE is complicated by the difficulty and delay in diagnosis and by its many different forms, not all of which should be treated in the same way. There is often concern for overtreatment. It has been stated that "nonconvulsive status epilepticus is underdiagnosed and potentially overtreated" *(48)*. The underdiagnosis part of the statement is certainly true. Overtreatment is an important concern, given the lesser consequences of NCSE in most cases (compared to those of GCSE) and potential complications of treatment. The good clinical judgment of a neurologist is a crucial.

In the idealized case, any form of NCSE is diagnosed readily and responds immediately to iv benzodiazepines. This is not a rare scenario, but it does not cover most patients. Episodes of typical ASE may resolve spontaneously, but even generally

benign episodes may end with a generalized convulsion *(8)*. Fortunately, given the relatively minimal evidence of ongoing neurologic damage or lasting neurologic deficits due to NCSE, treatment probably need not be as aggressive as for continuing GCSE. Many of the treatments cited from the literature required days to succeed, although this is not the recommended plan. Rarely will NCSE patients require aggressive treatments such as coma induced by pentobarbital, propofol, or ketamine, or higher doses of benzodiazepines.

While risks of treatment exist, there are many reasons for treating NCSE with AEDs expeditiously. The patients are clearly ill with ongoing seizures and have impaired consciousness and other neurologic deficits that are potentially reversible and certainly treatable. NCSE, like other forms of SE, also entails the attendant morbidity of incidental trauma, aspiration pneumonia, and so on. In addition, many episodes of NCSE begin with, and may end with, generalized convulsions, which are in turn potentially harmful. Finally, we must remain alert to the possibility that some prolonged episodes might cause lasting damage. Treatment should be individualized and judicious but should not be delayed *(5)*. NCSE remains an underdiagnosed, treatable condition and one well worth both diagnosing and treating.

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VI Pediatric and Neonatal Status Epilepticus

16
Status Epilepticus in Children

James J. Riviello, Jr.

Status epilepticus (SE) is a life-threatening medical emergency that requires prompt recognition and treatment. SE is not a specific disease but is a manifestation of either a primary central nervous system (CNS) insult, or a systemic disorder with secondary CNS effects. It is mandatory to look for an underlying cause, especially in younger children and infants, in whom symptomatic SE is more common. Identifying and treating the precipitating cause helps control seizures, prevents ongoing neurologic injury, and hopefully prevents seizure recurrence. Basic neuroresuscitation principles, the ABCs (airway, breathing, circulation), are the cornerstone of initial treatment. An organized and systematic treatment regimen, planned in advance, is needed, including one for refractory status epilepticus (RSE). Initial treatment follows the ABCs but, once stabilized, patient management may be individualized.

The following points are emphasized: definition; clinical and EEG stages; early treatment; special circumstances that may require immediate seizure control; and treatment of RSE. There are also unique syndromes of SE in children, including neonatal SE and electrical status epilepticus of sleep. Much SE research has been done in adults but can be applied to children *(1)*; we shall indicate if a study was done in children.

1. DEFINITIONS

Gastaut defined SE as "an epileptic seizure that is sufficiently prolonged or repeated at sufficiently brief intervals so as to produce an unvarying and enduring epileptic condition" *(2)*. Without a specific duration, this definition seems vague, but it allows a dynamic interpretation. Aicardi and Chevrie, in the first paper on pediatric status epilepticus in 1970, used a duration of 1 h *(3)*. Criteria for diagnosis apply to both adults and children. The Working Group on Status Epilepticus of the Epilepsy Foundation of America defined SE as more than 30 min of either continuous seizure activity or two or more sequential seizures without full recovery of consciousness between seizures *(4)*. Gastaut's definition may be applied to neonates, who typically do not have continuous seizure activity but have frequent seizures without recovery of consciousness.

SE is classified by seizure type, using the International Classification of Epileptic Seizures (ICES), based on seizure onset location and whether partial

From: *Current Clinical Neurology: Status Epilepticus: A Clinical Perspective*
Edited by: F. W. Drislane © Humana Press Inc., Totowa, NJ

Table 1
Etiologic Classification of Seizures and Status Epilepticus

Acute symptomatic: associated with an acute CNS insult
Remote symptomatic: seizure disorder or epilepsy in the setting of a past CNS insult
Remote symptomatic with acute precipitant: an acute insult (precipitant) superimposed on a past CNS insult
Progressive encephalopathy: associated with a progressive degenerative or metabolic disorder
Cryptogenic seizure: no etiology identified in a patient with an underlying neurologic disorder or abnormal neurologic examination
Idiopathic: no etiology identified in a patient with a normal neurologic history and examination (usually genetic)
Febrile: a subtype of idiopathic, associated with fever (after exclusion of an acute CNS infection or inflammation; meningtis, encephalitis, or inflammatory disease)
Pseudoseizures, pseudostatus epilepticus

(focal) or generalized *(5)*. A modified system is based on semiology *(6)*: convulsive (generalized tonic-clonic) SE (GCSE); nonconvulsive SE (NCSE); or simple partial (focal) SE. NCSE occurs with either generalized ("absence") or focal ("complex partial") epilepsy. SE occurs with any seizure type. A subtype of NCSE includes electrical status epilepticus of sleep (ESES). SE is also classified by etiology (Table 1): acute symptomatic, remote symptomatic, remote symptomatic with acute precipitant, progressive encephalopathy, cryptogenic, idiopathic, and febrile SE *(7)*.

GCSE consists of continuous tonic or clonic motor activity or both, which may be symmetric or asymmetric, overt or subtle, and has marked impairment of consciousness with bilateral, although frequently asymmetric, EEG ictal discharges *(6,8)*. NCSE has no outward clinical signs except altered awareness. The term subtle GCSE is used when there is impairment of consciousness with very subtle convulsive movements and evolves from prolonged convulsive SE or after unsuccessful treatment. ESES is associated with cognitive dysfunction, especially regression *(8)*. Classification also includes pseudoseizures, as pseudostatus epilepticus occurs in children *(9,10)*.

2. STAGES OF STATUS EPILEPTICUS

The clinical stages of SE are: premonitory (prodromal); incipient (0 to 5 min); early (5 to 30 min); transition, from the early to the later; established (30 to 60 min); refractory (greater than 60 to 90 min); and postictal *(11)* (Table 2). The premonitory stage consists of confusion, myoclonus, or increasing seizure frequency. The early stage includes continuous seizure activity, whereas subtle GCSE or NCSE may develop in the refractory stage. If a premonitory stage is identified, treatment should be initiated. SE is not considered refractory if therapy has been inadequate. Special circumstances may need immediate seizure control in the incipient stage (before a short seizure evolves into actual SE). We call these the special circumstances of the early stage (Table 3) *(12)*.

According to Treiman and colleagues, EEG stages correlate with clinical stages and may occur in a predictable sequence: (1) discrete seizures with interictal slowing;

Table 2
Clinical Stages of Status Epilepticus and Corresponding Time From Seizure Onset

Clinical Stages	Minutes
Premonitory	before SE
Incipient	0–5
Early	5–30
(Special circumstances: *see* Table 3)	
Transition	may vary
Late (established)	30–60
Refractory	60–90
Postictal	after SE

Modified from refs. *11,12*.

Table 3
Special Circumstances: Early Stage

Postoperative patients, especially with cardiac surgery and neurosurgery
Head trauma, increased intracranial pressure, brain tumor
CNS infections, especially meningitis or encephalitis
Organ failure, especially hepatic, or multisystem failure
Hyperthermia (may need specific treatment); malignant hyperthermia; hyperthyroidism
Metabolic disorders prone to develop increased intracranial pressure: diabetic ketoacidosis, organic acid disorders

Adapted from ref. *12*.

Table 4
EEG Stages of Status Epilepticus

1. Discrete seizures with interictal slowing
2. Merging seizures
3. Continuous ictal discharges
4. Continuous ictal discharges punctuated by flat periods
5. Periodic epileptiform discharges (PEDs)

Adapted from ref. *13*.

(2) waxing and waning of ictal discharges; (3) continuous ictal discharges; (4) continuous ictal discharges punctuated by flat periods; and (5) periodic epileptiform discharges (PEDs) on a flat background *(13)* (Table 4). Early antiepileptic drug (AED) treatment controls seizure activity better than when given in later stages *(13)*, but not every episode of SE passes through each stage *(14)*. The PED stage may also consist of either bilateral (BiPEDs) or lateralized (PLEDs) patterns *(15)*.

Typically, neonates (<1 mo old) are excluded from SE series because their seizures and EEG features are different (*see* Chapter 17). The Richmond SE database compared neonatal EEGs to those of 1- to 6-mo-old infants. Infants over 2 mo of age could generate prolonged seizures; focal seizures generally had a single focus and could lead to secondary generalization *(16)*.

3. TRENDS IN EVALUATION OF STATUS EPILEPTICUS

The clinical trend in the evaluation of SE has been to decrease the duration required for its diagnosis and to treat when it is unlikely that the seizure will stop. The 1993 working group recommended treatment after 10 min *(3)*. The VA Cooperative Study, which studied various "first-line" AEDs in adults, used 10 min. Lowenstein, Bleck, and Macdonald proposed an "operational definition" for GCSE in adults and older children (age >5 yr) and recommended treatment after 5 min of either a continuous seizure or two or more discrete seizures between which there is incomplete recovery of consciousness *(18)*. The San Francisco Pre-Hospital Treatment study in adults subsequently used 5 min *(19)*.

Clinical and experimental data support earlier treatment. In a prospective childhood study, seizure duration had a bimodal distribution: 3.6 min in one group (76% of cases) and 31 min (24%) in the other; thus, seizures are unlikely to stop when they last more than 5 to 10 min *(20)*. With initial treatment failure for SE in the VA Cooperative study, only 5.3% responded to the third AED *(17)*. There was a higher response rate in the Columbia Study when the third AED was given earlier *(21)*. The San Francisco Pre-Hospital Treatment study even showed a response to low-dose (2 mg) lorazepam, given in the field *(19)*.

Experimental models show a time-dependent treatment efficacy. In a self-sustaining model of SE induced by intermittent perforant path stimulation (PPS), both diazepam and phenytoin prevented SE when given 10 min prior to PPS *(22)*. The efficacy of both, however, decreased when given later; phenytoin was less effective when given at 40 rather than 10 min after PPS, while diazepam was less effective when given 10 min after PPS than as pretreatment. A loss of inhibitory $GABA_A$ receptors occurs over time in partial SE *(23)*, and in the lithium-pilocarpine model there is a functional change in $GABA_A$ receptors *(24)*. These studies help to explain the decreased benzodiazepine response *(24,25)*, which has also been demonstrated in young animals *(26)*. The response to treatment may vary depending on the EEG stage.

4. EPIDEMIOLOGY OF STATUS EPILEPTICUS

There have been four population-based studies of SE that included children *(27–31)*. The incidence in children was 41/100,000/yr in Richmond, Virginia *(28)*, 18/100,000 in Rochester, Minnesota *(29)*, 10/100,000 in Switzerland *(30)*, and 6.2/100,000 in California *(31)*. All show a higher incidence in the youngest children and in the elderly. The Richmond study stratified incidence by age: 156/100,000 in infants, 38/100,000 in pediatrics, 27/100,000 in adults, and 86/100,000 in the elderly *(28)*.

SE is common in childhood-onset epilepsy. In a study of 613 children with newly diagnosed epilepsy in Connecticut, 56 (9.1%) had one or more episodes of SE by the time the diagnosis was established *(32)*. In a population-based cohort of childhood epilepsy from Finland, 41 of 159 patients (27%) had SE *(33)*. SE was more likely within the first 2 yr after the epilepsy onset. Risk factors for SE included remote

symptomatic cause, age of onset 6 yr or younger, and partial seizures. Among 394 children with SE from Richmond and the Bronx, SE was common in younger children; over 40% occurred in those aged 2 yr or younger, and of these, more than 80% had a febrile or acute symptomatic etiology *(34)*. Cryptogenic or remote symptomatic etiologies were most common in older children, as was a prior history of epilepsy. In a prospective study from the Bronx, SE was recurrent in 16 of 95 patients (17%) *(35)*. Overall, neurologic abnormalities occurred in 34%, but abnormalities were present in 88% with recurrent SE (two episodes) and in all five patients with three or more episodes. The risk of recurrence varied by etiology: 4% in the idiopathic group, 44% in the remote symptomatic group, 3% in the febrile group, 11% in the acute symptomatic group, and 67% in those with progressive neurologic disorders.

5. ETIOLOGY AND PROGNOSIS

Prognosis of SE depends on etiology, age, duration, and treatment adequacy. The specific cause must be determined and treated, if possible, in order to prevent ongoing neuronal injury and facilitate seizure control. Etiology is a very important determinant of morbidity and mortality. In the classic paper of 239 cases of pediatric SE by Aicardi and Chevrie, 113 were symptomatic and 126 cryptogenic *(3)*. In those with symptomatic SE, 63 (56%) had acute CNS insults (including treatable disorders such as bacterial meningitis, encephalitis, dehydration or electrolyte disorders, toxic ingestions, or subdural hematoma), and 50 had a remote symptomatic cause, also referred to as a chronic encephalopathy (anoxia, progressive encephalopathy, nonprogressive encephalopathy, brain malformation, cerebral palsy, and Sturge-Weber syndrome). In those with cryptogenic SE, 67 (53%) were associated with fever (a prolonged, or complex, febrile seizure). Maytal and colleagues, in a more recent study in children, had similar figures for etiology: 45 of 193 (23%) had acute symptomatic and 45 of 193 (23%) remote symptomatic causes *(36)*.

The incidence of various causes differs in children and adults. In the Richmond study, the most common cause of SE in adults was cerebrovascular disease (25.2%), whereas fever or infection (35.7%) was most common in children *(37)*. Recent medication changes had occurred in 20% of children and 19% of adults (Table 5). Symptomatic SE has a maximum frequency in the very young and has a higher morbidity and mortality. It occurs less frequently after 1 yr of age *(38)*. Idiopathic SE is rare during the first several months but becomes more common after 6 mo. Treatable causes for seizures in 31 infants less than 6 mo of age presenting to the ED included: infections in 7% (one with pneumococcal meningitis); inborn errors of metabolism in 16%; electrolyte abnormalities in 16%; and trauma in 3% *(39)*. Maytal and colleagues reported a good prognosis with febrile SE (a subtype of idiopathic SE); outcome was related to seizure duration only in the symptomatic group, and sequelae were more likely in younger children *(36)*.

Pediatric SE mortality ranges from 3 to 11% and is also related to etiology and age *(3,36,40–46)*. In the Maytal study, overall mortality was 4%, occurring only in those with acute symptomatic or progressive symptomatic etiologies *(36)*. The lowest mortality, 3%, was from Saudi Arabia *(46)*. The Richmond study had an overall

Table 5
Comparison of Etiology in Children and Adults in the Richmond Study

Etiology (%)	Children (<16 yr)	Adults (>16 yr)
Cerebrovascular	3.3%	25.2%
Medication change	19	18.9
Anoxia	5.3	10.7
Alcohol/drug-related	2.4	12.2
Metabolic	8.2	8.8
Unknown	9.3	8.1
Fever/infection	35.7	4.6
Trauma	3.5	4.6
Tumor	0.7	4.3
CNS infection	4.8	1.8
Congenital	7.0	0.8

Adapted from ref. *37*.

mortality of 6% *(38)*. When stratified by age, the mortality within the first year was 17.8%, but 24% in the first 6 mo compared to 9% in months 6 to 12. The difference was attributed to a higher incidence of symptomatic SE in the youngest children *(38)*. With regard to morbidity, a Canadian study reported that 34% of 40 children with seizure duration of 30 to 720 min had subsequent developmental deterioration *(47)*. Prolonged SE itself may have an increased morbidity and mortality *(48)*. An increased morbidity and mortality also occurs with nonconvulsive SE, although this was related to duration (from 36 to >72 h) *(49)*. This increased morbidity with NCSE is controversial *(50,51)*.

Fever is a common precipitant of seizures in children. In the absence of an underlying infection, neurologic abnormality, or epilepsy, these are referred to as benign febrile seizures. Typically, they are short (<15 min), nonfocal, and not associated with a prolonged postictal state *(52)*. Febrile SE (FSE) is a subgroup common to children. In the Richmond series, the highest incidence of SE occurred in children with fever, 35.7% (vs 4.6% with fever in adults with SE) *(37)*. A symptomatic cause, especially meningitis or encephalitis, must be excluded in order to classify an episode as FSE. There is also controversy regarding prognosis. A study from Italy reported a high incidence of neurologic sequelae, especially seizures, with an early age of onset but did not exclude symptomatic cases *(53)*. Another study reported speech delay *(54)*. Maytal and Shinnar reported a better prognosis in the neurologically normal child *(55)*. The British National Cohort Study also found that the prognosis for lengthy febrile seizures and SE was determined primarily by the cause *(56)*.

In a study of GCSE treated in the Netherlands, a worsened prognosis of SE was related to the underlying etiology, seizure duration greater than 4 h, associated medical complications, and the quality of the medical care delivered *(57)*. Inadequate medical care included use of the wrong AED dose or route; an unnecessary delay in treatment; lack of mechanical ventilation despite respiratory insufficiency or when

associated medical complications occurred; and use of neuromuscular paralysis to treat seizures without EEG monitoring to determine if electrographic seizures persisted.

6. EVALUATION

Initial management starts with the ABCs (Table 6). Diagnostic studies are obtained after stabilization. Studies are selected according to history, examination, and age (Table 7), with a greater need to exclude treatable causes in the youngest children. Serum glucose should be checked with a dipstick to diagnose hypoglycemia rapidly. CBC may be helpful for infection, although leukocytosis can occur from SE itself. Electrolytes, calcium, phosphorus, and magnesium values may be helpful, especially if there has been preceding vomiting and diarrhea. The diagnosis of meningitis must be considered in all febrile seizures and lumbar puncture (LP) considered in the febrile patient. LP may not be necessary, depending on the clinical situation. If there is concern for increased intracranial pressure or for a structural lesion, LP can be deferred until after neuroimaging. Antibiotics can be given prior to LP, relying on the CBC and bacterial cultures. Cerebrospinal fluid (CSF) pleocytosis may occur without infection, presumably due to a breakdown in the blood-brain barrier *(58)*. In one study, the highest CSF WBC count from SE alone (without any acute insult) was 28/mm^3 *(59)*. If the patient is on AEDs, low levels may be associated with SE. In one study of 51 children, AED levels were therapeutic in only 66% *(60)*. Certain intoxications may predispose to GCSE or NCSE, especially theophylline *(42)* and isoniazid *(61)*, which is also associated with acidosis *(62)* and treated with pyridoxine (vitamin B6). Fatal SE has occurred with flumazenil, so it should be used with caution when there is a history of seizures, benzodiazepine use, or with a mixed overdose *(63)*.

In general, neuroimaging is indicated for new-onset SE, especially without a defined cause, or without prior epilepsy. The American College of Emergency Physicians (ACEP) practice parameter for neuroimaging in seizures *(64)* defined the following categories: "emergent" (scan immediately); urgent (scan included in the patient disposition plan, which may be set up but not done immediately); and routine (indicated but later). Emergency imaging is required for new-onset SE, or in a patient with known epilepsy who does not respond, but the patient must be stabilized first. There is a higher incidence of life-threatening lesions (hemorrhage, brain swelling, mass effect) with a first-time seizure or epilepsy with new focal deficits, persistent altered mental status (with or without intoxication), fever, recent trauma, persistent headache, cancer, anticoagulation, or AIDS. For pediatric seizures in general, a predisposing condition or focal seizure in a child less than 33 mo old has been associated with a high risk of an abnormal imaging study *(65)*. MRI is more sensitive, but often unavailable in emergencies, and CT scanning is adequate for life-threatening conditions. Usually, EEG is not needed initially. Indications for emergency EEG include unexplained altered awareness (to exclude NCSE); neuromuscular paralysis for SE; high-dose suppressive therapy for refractory SE; or when there is no improvement or return to baseline mental status after controlling overt

Table 6
Initial Management of the Incipient Stage

What to do first: The ABCs:
Stabilize and maintain the **A**irway
Establish **B**reathing (i.e; ventilation)
Maintain the **C**irculation
Monitor vital signs: pulse, pulse oximetry, respiratory rate, blood pressure, temperature, oxygenation
Position the head to prevent or relieve airway obstruction
Early intubation to protect airway, provide adequate O_2, and ventilation
Establish iv access
Check: Serum glucose, by blood or dipstick
CBC, differential
Chemistries: electrolytes, BUN, Cr, Ca, Phos, Mg
AED levels, if applicable
Toxicology studies

Table 7
The Need for Other Tests

Lumbar puncture (LP): to exclude meningitis, encephalitis, or subarachnoid hemorrhage. If concern for increased intracranial pressure (coma, focal neurologic examination, papilledema), should be deferred until cranial CT scan is done.
Electroencephalogram (EEG): Needed initially only if there is unexplained altered awareness, to exclude nonconvulsive status, or if the diagnosis is in doubt, especially for pseudoseizures, or when there has been no improvement in mental status within 30 min despite control of convulsive movements (to exclude NCSE).
Neuroimaging: Emergency neuroimaging with CT or MRI scan needed with unexplained SE, especially if new onset, focal, or associated with focal neurologic signs, or if there is concern for increased intracranial pressure before LP. This is done after the patient is stabilized.
Other laboratory studies: Serum ammonia, lactic acid, pyruvic acid, amino acids, organic acids, carnitine, acyl-carnitine, acyl-glycine obtained as needed. Consider especially when SE occurs in a child with previous, unexplained developmental delay.

convulsive movements (to exclude NCSE) *(66)*. NCSE occurred in 14% of patients treated for GCSE in one series *(67)* and was detected in 8% of all comatose patients in another *(68)*. EEG is also helpful when the diagnosis is in doubt, especially when pseudoseizures are being considered *(69)*.

7. THERAPY FOR STATUS EPILEPTICUS

The goal of therapy is to control seizure activity before neuronal injury occurs, especially before brain compensatory mechanisms fail. Irreversible damage may occur somewhere in the transition from the early to the refractory stage. Despite adequate oxygenation and ventilation this is between 30 and 60 min in experimental SE, and probably about 30 to 45 min in humans *(70)*.

Systemic and metabolic changes occur early, with increases in blood pressure, lactate, and glucose, and acidosis develops. Both respiratory and metabolic acidosis occur, although respiratory is more common *(71)*. Early on, brain parenchymal oxygenation, lactate, glucose, and oxygen utilization stay stable, and cerebral blood flow increases, but cerebral glucose decreases slightly. In later stages, blood pressure may be normal or decrease slightly, glucose may decrease, and hyperthermia and respiratory compromise may occur, leading to hypoxia and hypercarbia. Brain parenchymal oxygenation, cerebral blood flow, and brain glucose all decrease, contributing to an energy mismatch *(70)*. Serum neuron-specific enolase, a marker of brain injury, is elevated after both GCSE and NCSE *(72,73)*.

Most AEDs used to treat SE have the potential for respiratory and cardiac depression, especially when given by a loading dose (LD) *(74)*. Therefore, protecting the airway, controlling ventilation, and monitoring cardiac and hemodynamic function are mandatory. Intravenous (iv) administration is the preferred route for AEDs in SE, especially in the inpatient setting. If iv access is difficult, intramuscular (im), rectal, or intranasal routes have been used. The rectal route can also be useful if there is concern for side effects, particularly respiratory depression. Diazepam is the most widely used rectal AED in children.

8. PRIMARY AEDs FOR STATUS EPILEPTICUS

Phenobarbital, phenytoin, diazepam, and lorazepam have been the primary agents used for initial therapy (Table 8). Diazepam has a faster onset of action because of greater lipid solubility *(74)* but must be followed by another AED because seizure recurrence is common. This is especially so with acute symptomatic SE. In one adult study, only 9 of 20 patients had seizure control for greater than 2 h *(75)* and in another, only 5 of 15 had good seizure control for 24 h *(76)*. Lorazepam has longer anticonvulsant activity than diazepam because of a smaller volume of distribution *(77)*. It causes less respiratory depression and sedation, and seizure recurrence is less than with diazepam *(78)*. Lorazepam has been used in adults and children *(79,80)*. In 300 children with SE, the median lorazepam dose was 0.1 mg/kg, and SE was stopped in 79% *(81)*. In a double-blind study, seizures were controlled in 89% of episodes with 4 mg lorazepam, vs 76% with 10 mg diazepam—with similar times of onset and adverse events *(82)*. Midazolam may be given im if there is no iv access and causes less sedation and respiratory depression *(83)*.

Phenytoin may be given by an iv loading dose, in normal saline because it precipitates with dextrose. A LD achieves a therapeutic level rapidly without respiratory depression or sedation and provides for maintenance therapy *(84–86)*. Lack of sedation is important when mental status needs monitoring. The infusion rate should be no faster than 1 mg/kg/min in a child, not to exceed 25 mg/min, or 50 mg/min in the older child. Pulse and blood pressure should be monitored during the infusion. If hypotension occurs, the rate is decreased. In adults, a therapeutic level may be maintained for up to 24 h after a loading dose *(84)*, but it may not last this long in children *(87)*. A level obtained 2 h after loading guides the timing of maintenance phenytoin *(87)*.

Table 8
First-Line AEDs

AED	Dose	Rate	Max
Lorazepam	0.1 mg/kg	2 mg/min	8–10 mg[a]
Diazepam	0.2 mg/kg	5 mg/min	16–20 mg[a]
Fosphenytoin	20 mg PE/kg	up to 3 mg PE/kg/min	150 mg/min adult
Phenytoin	20 mg/kg	up to 1 mg/kg/min	50 mg/min adult 25 mg/min child 20mg/min elderly
Phenobarbital	20 mg/kg	1 mg/kg/min	100 mg/min adult 30 mg/min chil

[a]These maximum doses are guidelines only. There is no maximum dose, if one is prepared to maintain ABCs.

Intravenous phenytoin has an alkaline pH and is dissolved in solvents that cause vascular irritation, cardiac depression, and hypotension. "Purple glove syndrome," consisting of distal limb edema, discoloration, and pain, may occur following iv phenytoin infiltration; treatment may require fasciotomy or even amputation. In one series, purple glove syndrome occurred in 9 of 152 patients *(88)*. In a prospective series it occurred in only 3 of 179 *(89)*, but it has even occurred after oral dosing in a child *(90)*.

The phosphate-ester prodrug of phenytoin, fosphenytoin, is dosed as phenytoin-equivalents (PE), at 20 mg PE/kg. It can be given with dextrose solutions. Fosphenytoin is water-soluble and may given by the im route; paresthesia and pruritis may occur at the injection site. Fosphenytoin is converted rapidly to phenytoin by serum and tissue alkaline phosphatases *(91)*. Bioavailability is the same as with phenytoin, and the half-life for conversion is 7 to 15 min *(92)*. It may be difficult to maintain therapeutic levels in infants, and additional doses may be needed *(93);* subtherapeutic free phenytoin levels also occur in older children *(94)*. A 2 h phenytoin level is suggested to ensure conversion *(94)*. Side effects are more likely with hypoalbuminemia, renal failure, or hepatic failure, all of which cause higher free phenytoin levels. In this situation, the rate should be decreased by 25 to 50% *(91)*. (Intravenous phenytoin is no longer available at Children's Hospital, Boston.)

Phenobarbital has been used for SE at all ages. Although still considered the drug of choice for neonatal seizures, it has equal efficacy with phenytoin *(95)*. Respiratory depression and sedation occur, and caution is needed, especially when it is given in combination with other sedative AEDs, such as benzodiazepines. In a randomized trial of diazepam and phenytoin vs phenobarbital (10 mg/kg iv), phenobarbital had a shorter median time to seizure control (5 vs 9 min) and response latency (5.5 vs 15 min), with a similar incidence of intubation, hypotension, and arrhythmia *(96)*. The loading dose for phenobarbital is 20 mg/kg, administered at a rate no greater than 100 mg/min in older children and adults and 20 mg/kg in the neonate *(97)*.

9. SECOND-LINE AGENTS

Intravenous sodium valproate is available *(98)*. Previously, valproate was given by the rectal route. Although not FDA-approved for SE, it is used, especially if other agents fail. In children, loading doses have been from 10 to 30 mg/kg, with most using the higher ranges; an infusion rate of 1 mg/kg/h was not associated with serious side effects *(99)*. A 20 mg/kg loading dose should achieve a level of 75 mg/L *(100)*. It is safe in adults and children *(101,102)*. Hypotension occurred in a child at a rate of 30 mg/kg/h (0.5 mg/kg/min) *(103)*. A loading dose of 10 to 25 mg/kg, over 30 min, has been used in neonates *(104)*.

10. SPECIFIC TREATMENT SEQUENCES

Standard treatment guidelines established in advance of medical emergencies improve the quality of emergency care *(105,106)*. In a survey of the UK Intensive Care Society, however, only 12% of respondents used a specific protocol *(107)*. The working group on SE of the Epilepsy Foundation of America devised a treatment guideline that applied to all ages (except neonates) that is currently under revision. Time sequences in these guidelines are calculated from the seizure onset. They assume that brain compensatory mechanisms protect against neuronal injury from seizures initially, especially when there is hypertension with increased cerebral blood flow. Lothman outlined systemic and brain metabolism alterations that occur with prolonged SE *(70)*: hypoxemia, hypercarbia, hypotension, and hyperthermia, with a decreased brain oxygen tension, mismatch between the sustained increase in oxygen and glucose utilization and a fall in cerebral blood flow, and depletion of brain glucose and oxygen.

Treatment guidelines, especially for incipient and early stages, assume that compensatory mechanisms remain intact. Compensation requires adequate airway, breathing, circulation, and cerebral blood flow, and there are situations in which these mechanisms may be compromised. A study of *de novo* onset inpatient SE found a very high mortality (61%), suggesting that those with underlying illnesses are compromised and at a higher risk *(108)*.

Compensatory mechanisms, however, may be exhausted in already compromised situations, and if seizures continue after initial therapy, certain special circumstances may require a change in plans and more immediate seizure control. Also, there are maximum AED infusion rates, and in special circumstances, the infusion time may be too long. For example, with a maximum fosphenytoin infusion time of 150 mg PE/min, the infusion time is approx 7 min in a 50 kg child. In this situation, lorazepam is given first, but if seizures do not stop within 5 to 10 min, an intravenous agent such as thiopental, propofol, or pentobarbital is given to stop the seizure immediately. If there is hemodynamic instability, one may consider ketamine or use other agents to treat the hemodynamic instability. Propofol can be given as an acute bolus, but there are problems with prolonged infusions or higher infusion rates *(109)*. Intubation is done to maintain and protect the airway.

There have been only a few randomized clinical trials for SE—and none in children. A practice parameter for childhood SE is now under development in the

Table 9
Initial AED Treatment Sequence for SE (Code Team Manual, Children's Hospital, Boston)

5 min:	Lorazepam: 0.1 mg/kg (usual maximum 4 mg/dose); if no IV access: diazepam, 0.5 mg/kg/dose (max 20 mg) per rectum
10–15 min:	Lorazepam, 0.1 mg/kg/dose and start fosphenytoin 20 mg PE/kg (if fosphenytoin not available, use phenytoin 20 mg/kg)
15–20 min:	If seizures persist, phenobarbital 20 mg/kg
20–30 min:	If seizures persist, fosphenytoin, 10 mg PE/kg

Treat metabolic derangements as identified: hypoglycemia, hyponatremia.
Consider pyridoxine (vitamin B_6) for infants and children, especially with underlying epilepsy.

United States. In the UK, a four-step guideline has been devised for children and implemented in three centers *(106)*. The steps are: (1) lorazepam, 0.1 mg/kg iv or (if there is no iv access) rectal diazepam, 0.5 mg/kg; after 10 min: (2) lorazepam, 0.1 mg/kg; if seizures continue after another 10 min: (3) phenytoin, 18 mg/kg, or (if already on phenytoin) phenobarbital, 20 mg/kg and paraldehyde, 0.4 ml/kg rectally (after 20 min, consider pyridoxine for a child under 3 yr of age); if seizures continue 20 min after step 3 was started: (4) thiopental, 4 mg/kg iv. The initial treatment sequence in the Code Team Manual, Children's Hospital, Boston *(110)* is detailed in Table 9. We recommend fosphenytoin over phenytoin because of the potential cardiovasuclar side effects (including hypotension) and the concern for soft-tissue infiltration and injury with phenytoin, such as purple glove syndrome *(88–89)*.

Two pediatric centers have published results of their treatment protocols. Erikkson and Koivikko reported an overall response rate of 99% to diazepam, repeat iv AED, or thiopental *(111)*. Garr and colleagues reported a 94% response to diazepam, followed by phenytoin and paraldehyde *(112)*; 69 patients (85%) responded to a single dose of diazepam (rectal in 41 and iv in 28). Many guidelines use a repeat benzodiazepine dose, but in this study a repeat diazepam dose controlled seizures in only two additional children. Seizures stopped in 5 of 10 children receiving combined paraldehyde and phenytoin; nine (11%) required the ICU, five for persistent seizures and four for respiratory depression.

Several treatment surveys have been done. The UK survey of all ages showed that first line therapy was frequently a benzodiazepine with phenytoin *(107)*. In a US survey of 106 neurologists, 76% used lorazepam first; 95% would then use phenobarbital or phenytoin if lorazepam failed *(113)*. Epileptologists were surveyed to establish consensus guidelines for first-line, second-line, and third-line therapies for various epilepsy syndromes *(114)*. A treatment of choice was determined if selected by greater than 50%. Lorazepam was considered the treatment of choice for generalized convulsive, focal, and absence SE, with diazepam or phenytoin considered first-line for generalized convulsive and focal SE; diazepam and sodium valproate were considered first-line for absence epilepsy *(114)*. Prior to the VA Cooperative Study, the Working Group suggested either lorazepam or diazepam as first-line therapy, but now lorazepam is used first by many. For children, we advocate lorazepam

first, 0.1 mg/kg, with a maximum dose of 4 mg when iv access is available; if not, diazepam or lorazepam can be given rectally, or fosphenytoin and midazolam given intramuscularly. One review found no evidence that iv lorazepam is better than diazepam in children *(115)*, and another showed equal efficacy *(116)*.

11. REFRACTORY STATUS EPILEPTICUS

Refractory status epilepticus (RSE) occurs when seizures persist despite adequate treatment. By this time, the airway should be protected, ventilation controlled with intubation, circulation maintained, and transfer to the critical care unit should be in progress, or already done. The mortality in children with RSE varies from 16 to 43.5% *(7,117,118)*. A meta-analysis of RSE by Gilbert and colleagues identified 111 children treated with intravenous or inhalational anesthesia and found an overall mortality of 16% *(117)*, whereas in a series of 23 children by Kim and colleagues, the mortality was 43.5% *(118)*. Our data in children show that etiology is important for prognosis *(7)*. If convulsive activity has stopped but mental status does not improve, NCSE must be excluded—either by EEG, if available, or by empiric treatment if not.

If SE persists for >1 h despite adequate doses of conventional AEDs, high-dose suppressive therapy with iv anesthetic agents should be used. The treatment goal is to stop SE immediately and prevent seizure recurrence. Pentobarbital has been the most widely used agent *(119–125)*, given at 2 to 10 mg/kg, followed by a continuous infusion. Midazolam has a shorter half-life and causes less sedation *(83,126–132)*. High-dose phenobarbital causes less cardiovascular depression than pentobarbital *(133,134)* but has a longer half-life. High-dose diazepam has also been used *(135,136)*. In childhood SE, Singhi and colleagues reported equal efficacy of continuous diazepam and midazolam infusions, but midazolam led to more seizure recurrence *(135,136)*.

Other agents include lorazepam *(137)*, thiopental *(138)*, lidocaine *(139–142)*, inhalational anesthetics including isoflurane (Forane) *(143,144)*, and propofol *(145)*. Lidocaine may produce a paradoxical response, allowing focal seizures to generalize *(142)*.

Propofol has two main advantages: a rapid onset and a short duration of action. One study showed equal efficacy with pentobarbital, but propofol controlled SE in 2.6 min vs 123 min with pentobarbital *(145)*. Propofol may cause metabolic acidosis with prolonged use in children *(146–147)*, and adult deaths have occurred with high infusion rates *(148)*. This is called the propofol infusion syndrome *(149)*. Even in an adult study showing equal efficacy for seizure control, propofol was associated with a 57% mortality, vs 17% with midazolam *(129)*. As such, propofol should be used with caution, especially in children, ideally for a short time only, and the infusion rate should not exceed 67 μg/kg/min *(109)*. Immediate seizure control can be achieved and then another agent used for long-term seizure suppression.

Ketamine may be of value and it is a neuroprotective agent *(150–152)*. Chlormethiazole *(153)*, etomidate *(154)*, and clonazepam *(155)* are used in Europe. Paraldehyde *(156)* and chloral hydrate *(157)* may be given rectally, although paraldehyde is no longer available in the United States. Hypothermia *(158)* and vagus nerve stimulation *(159)* have also been used.

No prospective study has yet been done in refractory SE. In a systematic review of refractory SE, pentobarbital was associated with better seizure control than propofol or midazolam *(160)*. In the UK survey of 408 intensivists, 142 (35%) would use a benzodiazepine infusion if first-line treatment failed, and 130 (32%) would use a general anesthetic. If seizures continue, 333 neurologists (82%) would use thiopental and 56 (14%) propofol *(107)*. In the consensus guidelines, the drug of choice for "therapeutic coma" in GCSE and focal SE was pentobarbital; first-line agents were midazolam and propofol; for "absence" (presumed generalized NCSE), pentobarbital was the drug of choice, with no other first-line options, and midazolam was considered second-line *(114)*. In the US survey, when GCSE was refractory to two AEDs, 43% of respondents gave phenobarbital, 16% valproate, and 19% pentobarbital, midazolam, or propofol by a continuous infusion *(113)*.

Whether clinical seizures alone, or both clinical and electrographic seizures, need complete control is controversial *(161,162)*. Many use high-dose suppressive therapy with a burst-suppression pattern on EEG and aim for complete control of both clinical and electrographic seizures. Some aim for control of clinical seizures only, without EEG monitoring. In the US survey, 56% of respondents titrated the intravenous infusion to burst suppression on the EEG, whereas 41% used clinical seizure elimination as the endpoint *(113)*. Even if a burst-suppression pattern is the goal, the degree of suppression needed is unclear. We have aimed for a burst-suppression pattern with an interburst interval of at least 5 s *(7,163)*. In an analysis of the depth of EEG suppression with barbiturate anesthetics (pentobarbital or thiopental) in adults, persistent seizure control was better with electrocerebral inactivity on EEG (17 of 20 patients controlled) than with a burst-suppression pattern (6 of 12 patients) *(164,165)*. In another study of midazolam infusion to eliminate all clinical and electrographic seizures (reaching burst suppression only if needed), acute treatment failure occurred in 18%, breakthrough seizures in 56%, posttreatment seizures in 68%, and ultimate treatment failure in 18% *(130)*. Breakthrough seizures occurred in only 4% when the goal was EEG background suppression but in 53% when the goal was seizure suppression only. Hypotension, however, occurred more frequently with titration to background suppression *(160)*.

Prolonged high-dose suppressive therapy can be effected *(7,163,166)*, usually with various AED combinations. Such therapy is usually used for 12 to 24 h initially. The infusion is then tapered, and the sequence is started again if SE recurs *(7,166)*. Mirski and colleagues recommended prolonged therapy if there was a potentially good prognosis, i.e., in a healthy patient (no premorbid illness) with a self-limited disease, and with neuroimaging not indicating a poor prognosis *(167)*. We have treated children for up to 146 d *(7)*. A 26-yr-old with encephalitis was treated for 11 mo *(168)*. In our experience with children, no survivor of acute symptomatic refractory SE (of seven patients) returned to baseline, and all subsequently developed refractory epilepsy: seizure recurrence upon tapering in two, and within 1 to 16 mo in the other five *(166)*. In our entire group with refractory SE, 7 of 22 (32%) returned to baseline *(7)*. In the systematic review of adults, only 29% (48 of 164) returned to baseline *(160)*.

12. PREHOSPITAL TREATMENT OF STATUS EPILEPTICUS

The premonitory or incipient stage of SE can now be treated at home with rectal, buccal, or nasal AEDs, and iv AEDs can be given in the field. A prospective prehospital treatment study in adults randomized intravenous treatment to 5 mg of diazepam, 2 mg of lorazepam, or placebo, and showed that lorazepam was more effective than diazepam in terminating SE (59% response to lorazepam vs 43% with diazepam and 21% placebo [$p = 0.001$]) *(19)*. A retrospective study of GCSE in 38 children showed that prehospital (rectal or iv) diazepam resulted in a shorter seizure durations (32 min vs 60 min) and less seizure recurrence in the emergency department than for children without such prehospital treatment (58 vs 85%), and there was no difference in intubation rates *(169)*.

Rectal diazepam can be given at home for SE or serial seizures. The maximum dose is 10 mg in children. Although not FDA-approved for SE, we use it for home treatment but do not typically use it in the emergency department or for inpatient SE. The rectal gel preparation is easier to administer at home. Several other routes are used for benzodiazepines when there is no iv access. Sublingual lorazepam or intranasal or buccal midazolam can be given *(170,171)*, with rapid buccal absorption documented by levels *(172)*. Intranasal midazolam (0.2 mg/kg) has equal efficacy with iv diazepam (0.3 mg/kg) for prolonged febrile seizures *(173)*. Buccal midazolam (10 mg) and rectal diazepam (10 mg) have equal efficacy for seizures greater than 5 min *(172)*. They may also be given by intraosseous infusion.

13. SPECIAL SYNDROMES OF STATUS EPILEPTICUS: LANDAU-KLEFFNER SYNDROME

SE is classified as either convulsive or nonconvulsive, depending on whether there are convulsive motor movements. The two have similar treatments. There are also specific epileptic syndromes with sleep-activated epileptiform activity that may occur continuously, mimicking electrographic status epilepticus *(174)*, and appearing as if they are NCSE. This marked sleep activation on EEG is referred to as electrical status epilepticus of sleep (ESES), or continuous spikes and waves of slow sleep (CSWS) *(175,176)*. Despite the electrographic SE, clinical seizure activity is not present at the time.

Children with ESES typically present with regression in their cognitive abilities, either a language regression in Landau-Kleffner syndrome (LKS) *(174,177)* or a more global neuropsychiatric regression, the specific epileptic syndrome of ESES *(174–176)*. Both have the EEG pattern of ESES and are associated with marked behavioral problems in addition to the regression. Although they are considered epileptic syndromes, not all affected children have overt clinical seizures. The term "epileptiform encephalopathy" has been used when cognitive dysfunction (rather than actual clinical seizures) is the primary clinical deficit associated with the epileptiform activity *(174)*. Cognitive regression should raise concern for ESES, especially in children with underlying developmental problems. Although these disorders may respond to treatment with standard AEDs, other treatments are used, such as high-dose

benzodiazepines *(178,179)*, corticosteroids *(180)*, or other immune-modulating therapies, such as intravenous gamma-globulin (IVIG) *(181)*.

LKS is a rare epileptic syndrome, representing only 0.2% of pediatric epilepsies *(182)*. Its onset is usually in children older than 4 yr *(183)*. It may first manifest as an apparent word deafness, a "verbal auditory agnosia." Seizures and behavior disturbances, particularly hyperactivity, each occur in approximately two thirds of children with LKS *(174)*. Most LKS is idiopathic, but any pathologic process affecting the auditory cortex may cause it. We have had children with "symptomatic" causes of LKS, one with a left temporal lobe tumor and another with a left middle cranial fossa arachnoid cyst. Other causes include infectious disorders, such as cysticercosis and toxoplasmosis; inflammatory disorders, such as CNS vasculitis; demyelinating disease; and tumors such as temporal lobe astrocytomas and dysembryoplastic neuroepithelial tumors (DNET). Therefore, neuroimaging is warranted.

The classic features of LKS include a previously normal child with normal language acquisition, followed by a verbal auditory agnosia (word deafness), language regression, seizures, and an epileptiform EEG. An important corollary is intact peripheral hearing. Those without all the classic features but with the sleep-activated epileptiform EEGs have been referred to as LKS variants *(184)*. Variants include children without clinical seizures but with abnormal EEGs; children with involvement of more anterior language areas with dysfunction characterized by oral-motor apraxia, siallorhea, seizures, and an abnormal EEG (centrotemporal spikes similar to those seen with benign focal epilepsy); children with pervasive developmental delay (PDD; autism) with language regression and abnormal EEGs; and even children with congenital aphasias, also called developmental language disorders, with epileptiform EEGs.

The EEG in LKS shows bilateral, multifocal spikes and spike-and-wave discharges, occurring usually in the posterior regions (especially temporal or parietal), with a marked activation during sleep. Discharges can occur in many locations and may even be generalized. Some centers require the presence of ESES to make the diagnosis of LKS, but we do not consider ESES mandatory for diagnosis. The EEG may improve over time, either spontaneously or with treatment *(185,186)*. The EEG abnormalities in LKS may be an epiphenomenon *(187)*.

The evaluation of LKS should include a baseline history, physical examination, sleep-deprived EEG, formal neuropsychologic evaluation, neuroimaging (with MRI preferred), long-term video EEG monitoring (LTM) if needed, quantitative EEG with spike mapping, functional neuroimaging with either single photon emission computed tomography (SPECT) or positron emission tomography (PET) scan, and frequency-modulated auditory evoked response (FM-AER). The FM-AER tests receptive language function and is usually absent with a verbal auditory agnosia *(188)*. All children should have intensive speech therapy. Specific treatment for LKS is outlined in the next section. Standard AEDs may control seizures but do not appear helpful in the language disorder, for which steroid therapy is required.

In their original paper, Landau and Kleffner reported a positive relationship between treatment with AEDs and aphasia improvement *(177)*. In 1967, Deuel and

Lenn reported a case with a clear relationship between AED treatment and language improvement *(189)*, and there have been subsequent reports of improvement with various AEDs. It is unclear whether any one AED is better than others. Both carbamazepine and valproate have been used widely. We prefer valproic acid because of its better ability to suppress spike activity. Theoretically, it may have both anticonvulsant and antiepileptogenic properties. Anticonvulsant refers to suppression of seizures, whereas antiepileptogenic refers to suppression of the development of epilepsy or the underlying process that leads to epilepsy *(190)*. Valproate appears to be a better spike suppressor than other AEDs and may normalize EEGs. Carbamazepine may worsen some generalized epilepsies and may even worsen focal spike-and-wave discharges and activate the EEG *(191–193)*. Lamotrigine is also a good spike suppressor *(194)*, but we have seen children worsen with every AED we have used.

The prognosis for LKS varies, depending on the series. In a follow-up of nine of the original Landau and Kleffner patients after 10 to 28 yr in 1980, four had full recovery, one a mild language disability, and four had moderate disability *(195)*. Later papers have not been as positive. Bishop did a literature review of 45 LKS patients *(183)*. Age of onset seemed related to the outcome—less favorable if the onset occurred before 4 yr of age. Deonna and colleagues reported that only one of seven adult patients had normal language, with the other six demonstrating varying degrees of language deficits, some with complete absence of language *(196)*. A recent paper on neuropsychologic follow-up reported that nine of 12 LKS patients had persistent language deficits of different degrees *(197)*.

14. SPECIAL SYNDROMES OF STATUS EPILEPTICUS: CONTINUOUS SPIKE WAVES OF SLEEP

ESES, or CSWS, is also rare, occurring in only 0.2% of pediatric epilepsies *(182)*. Strict definition of ESES requires sleep-activation epileptiform activity in 85% of slow-wave sleep *(175,176)*. There are symptomatic and cryptogenic cases, determined by etiology and whether normal neurologic or psychomotor development was present before the onset of the CSWS.

These children commonly have seizures, although they may be infrequent. The hallmark of this syndrome is regression in cognitive functioning and behavior, but not primarily in language as in LKS. Tassinari and colleagues reported 29 children with CSWS *(176)*. All except one had seizures; one had a single seizure, and one had only three seizures. Eighteen had normal and 11 abnormal psychomotor development prior to onset. In the 18 with normal development, all had severely lowered IQ and behavioral disturbances, defined as decreased attention span, hyperactivity, aggression, and difficulties with interaction and inhibition, and two patients developed a psychotic state. In the 11 with abnormal psychomotor development, mental deterioration occurred in all; three developed a marked hyperactivity, and one showed "massive regression," including regression in language, and a loss of interest in all activities.

One must distinguish the EEG finding of ESES from the epileptic syndrome of ESES (CSWS). The first describes the sleep-activated EEG. The epileptic syndrome

Table 10
Prednisone Dose for LKS, ESES

Month 1	2 mg/kg daily
Month 2	1.5 mg/kg daily
Month 3	1 mg/kg daily
Month 4	1 mg/kg, every other day
Month 5	0.5 mg/kg every other day
Month 6	0.25 mg/kg every other day

includes the EEG findings plus the associated clinical characteristics *(198)*. The EEG pattern of ESES may occur in LKS. The clinical pattern may depend on the characteristics of the EEG findings: with a more focal ESES, language regression may predominate, whereas with a more generalized EEG pattern, neurobehavioral dysfunction predominates *(199)*. LKS and ESES have been called "benign" because the EEG may improve over time. Given the devastating neuropsychologic deficits that may be seen in these epileptiform encephalopathies, we consider them "malignant" epileptic syndromes.

Treatment of LKS and ESES is similar. Specifics are debated. Although there appeared to be a relationship between AEDs and aphasia improvement in the original LKS report *(177)*, more recent studies imply that AEDs control seizures but not the aphasia *(180,200)*. McKinney and McGreal reported a better response with steroids *(201)*. Some children have improved after steroid therapy who had not responded to AEDs *(180,200)*. They also thought that the rapidity of the response and sequelae depend on the duration and severity of symptoms prior to treatment, that initial high doses are more effective, and that brief treatment is ineffective or leads to a high relapse rate. For ESES, valproic acid, benzodiazepines, ethosuximide, and lamotrigine have been the most successful AEDs *(176)*. Again, carbamazepine may worsen the EEG *(191–193)*.

We have analyzed our experience with ESES treatment in 12 children *(202)*. Only one responded to initial therapy with valproic acid *(202)*, and there was a high rate of relapse with steroid therapy, even when prolonged. In general, for either LKS or ESES, if AEDs do not work, high-dose corticosteroids are used. In most cases, steroids appear to work through GABAergic effects, rather than by immune mediation *(203)*. We have modified the high-dose diazepam protocol for ESES introduced by De Negri and colleagues *(178)*, using 1 mg/kg, either orally or rectally, under EEG guidance, followed by 0.5 mg/kg, orally, for 3 wk *(179)*, followed by a taper of 2.5 mg/kg/mo. Every patient has eventually developed epileptiform activity again, and all have responded to a repeat course of treatment. We now continue maintenance diazepam in those who have responded. The best responses occur in children with idiopathic LKS.

Both ACTH and prednisone have been used. Options include a short course of steroids or longer treatment. Even using a high dose, prolonged protocol, we have had relapses in four of five children, although they subsequently responded to repeat treatment with a slower tapering schedule *(202)*. We generally use prednisone, for 6 mo, following the dose schedule in Table 10.

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17
Status Epilepticus in Neonates

John N. Gaitanis and James J. Riviello, Jr.

Neonatal status epilepticus (NSE) is distinct from status epilepticus (SE) at later ages. This distinction pertains to all aspects of the disorder, including its definition, etiology, EEG features, treatment, and prognosis. In fact, NSE bears greater resemblance to neonatal seizures than it does to SE in older populations. This chapter will outline the unique features of NSE, highlighting aspects that differ from SE in older age groups, and will provide recommendations for its diagnosis and treatment.

1. WHY NEONATAL SEIZURES DIFFER

Neonatal seizures and NSE are unique because the neonatal brain differs in both structure and physiology from the brains of older children and adults. Although the basic organization of the cortex (lamination) is in place, dendritic growth, axonal-dendritic connections, and synaptic stabilization are not complete in the newborn *(1,2)*. Likewise, myelination is immature, preventing the rapid, well-organized spread of epileptic discharges *(3)*. Physiologically, excitatory mechanisms (primarily mediated by glutamate) predominate over inhibitory γ-amino butyric acid (GABA) inputs *(1)*. The end result of these differences is that epileptic activity develops more easily in newborns than in adults, and seizures, once they occur, spread less readily.

Neonatal seizures often lack a clinical correlate. In one study, only 21% of neonates had a clinical correlate during electrographic seizures *(4)*. A separate report found that only 45% of preterm and 53% of full-term neonates demonstrated clinical signs coincident with their electrographic seizures *(5)*. The lack of clinical manifestations during an electrographic seizure implies that the involved region of cortex does not serve an obvious function. Moreover, when neonatal seizures are recognized, they often have subtle manifestations, including such unobtrusive signs as autonomic phenomena, apnea, and oral-buccal-lingual or oculomotor movements. Such manifestations imply a subcortical generator *(1)*—which is possible considering that the neonatal limbic, diencephalic, and brainstem structures are more mature than the neonatal neocortex.

Further complicating the assessment of neonatal seizures is the frequent absence of an electrographic correlate to a clinical event. Mizrahi and Kellaway found inconsistent or no electroencephalogram (EEG) changes at the time of clinical events in 48 of 71 newborns *(6)*. Focal clonic seizures had a consistent electrographic correlate,

From: *Current Clinical Neurology: Status Epilepticus: A Clinical Perspective*
Edited by: F. W. Drislane © Humana Press Inc., Totowa, NJ

Table 1
Classification of Neonatal Seizures

Clonic
Focal
Multifocal
Tonic
Focal
Generalized
Myoclonic
Focal
Multifocal
Generalized
Subtle

Adapted from ref. *1*.

but subtle seizures did not. In that study, neonatal seizures with a consistent electrographic signature were presumed to have an epileptic pathophysiology, whereas seizures without an electrographic signature were considered nonepileptic events *(6)*. Yet seizures exhibiting electroclinical dissociation may arise from foci not consistently reflected in surface electrodes *(7)*. Therefore, the absence of a surface correlate does not exclude an epileptic mechanism.

Because of these clinical differences, neonatal seizures require a separate classification system from that used for seizures in older children and adults. Volpe has devised the most commonly used classification system for neonatal seizures, based on seizure semiology *(1)* (Table 1). Four basic seizure types are described: subtle, clonic, tonic, and myoclonic. Within these, there are subheadings describing whether the seizure is focal (involving only one site), multifocal (involving more than one site or having a migratory spread), or generalized. The heading "subtle" is unique to neonates and includes clinical manifestations such as autonomic phenomena, apneic episodes, oral-buccal-lingual or ocular movements, and certain limb movements. Subtle seizure manifestations are more common in premature infants *(8,9)*.

Just as seizures differ between neonates and older populations, so does SE. Two studies support the concept that NSE is fundamentally different from SE in children and adults. Morton and colleagues, using the Richmond database, assessed maturational changes occurring in the EEG of SE through the first 6 mo *(10)*. The EEGs of neonates with NSE showed brief, partial, serial seizures with multiple foci (mean of 3.4 foci per EEG), with 22.6 seizures per hour, lasting a mean of 94.5 s. In the 1-to-6 mo group, children older than 2 mo were capable of having prolonged seizures; partial seizures typically had one focus and secondary generalization occurred. Between 1 and 2 mo of age, 9 of 12 patients had only brief, focal, intermittent seizures (10 s to 5 min duration) and 3 of 9 had 2 or more independent seizure foci with independent simultaneous seizures. With regard to the traditional concept of SE, this study suggests that ages between 1 and 2 mo represent the transition point from NSE to SE in the older infant, and that by 2 mo of age, the usual adult concept of SE applies.

Mikati and colleagues *(11)* studied the stages of SE defined by Treiman and colleagues *(12)*, in the developing brain, comparing the stages of SE in postnatal day (P) 15 and P35 rats. (In experimental animal work, the term *postnatal day* is used to define comparable ages between the experimental animal and the human; the P15 group is similar to the postnatal human, and the P35 group is similar to the prepubescent human.) The behavioral manifestations of seizures in the P15 group did not segregate into distinct stages, and although all five of Treiman's EEG stages were present, the P15 rats were less likely to progress through all the stages. Thus, both clinical research and animal models support the notion that NSE is distinct from SE in older populations.

2. DEFINITIONS

NSE lacks a single widely accepted definition. Many studies of SE have excluded children under 1 mo of age, and those that do include neonates differ in their criteria for diagnosing NSE *(13–18)* (Table 2). Some have used only clinical criteria; others employ electrographic data. Establishing a widely accepted definition for NSE is important to ensure consistency among studies, allowing for comparison of treatment and outcome data.

The clinical and electrographic criteria for NSE have been evolving. Monod et al. and Udaeta Mora et al. both included repetition of clinical or subclinical seizures in a newborn with an abnormal interictal neurologic state *(13,14)*. Udaeta Mora added the following EEG characteristics: generalized high-voltage paroxsysmal discharges, with two or more discharges occurring every 10 s for at least 20 min. Scher and colleagues defined NSE as continuous seizure activity for at least 30 min or recurrent seizures for at least 50% of a 1- to 3-h recording time *(16)*. Wertheim and colleagues referred to continuous seizure activity in one or more EEG channels for at least 4 h, or separated for only a short period by activity with frequent sharp waves or spikes *(17)*. Ortibus and colleagues referred to a seizure duration greater than 30 min, or seizures and periodic discharges exceeding 50% of the EEG recording *(18)*. Such variation in definitions makes it difficult, if not impossible, to compare findings among studies *(18)*. Clancy used the term *sharp epileptiform transients* (SETs) to refer to frequent spike or sharp waves occurring between overt clinical and electrographic seizures *(19)*; for the purposes of determining a time abundance of epileptiform activity in the various definitions of NSE, SETs are equivalent to periodic discharges.

Adult definitions of SE have not been useful in clarifying these inconsistencies because many are not applicable to the newborn population. For example, much of the existing work on SE centers on generalized convulsive status epilepticus (GCSE) *(20–22)*, but newborns rarely have well-organized generalized tonic-clonic seizures *(1,6,16)*. Also, adult studies have defined SE as 30 min of continuous seizure activity *(20,21)*, but neonates infrequently develop seizures of this duration. Clancy and Legido measured the duration of neonatal seizures and reported most to be brief, lasting just more than 2 min on average *(23)*. Solitary prolonged seizures were infrequent. Of 487 seizures recorded, 97% lasted under 9 min, and the longest was 45 min. Scher and colleagues recorded the average ictal duration in full-term infants as

Table 2
Definitions of Neonatal Status Epilepticus

Author	(Reference)	
Monod	*(13)*	Repetition of clinical or subclinical convulsions with abnormal interictal neurologic status, occurring for at least a few hours.
Udaeta Mora	*(14)*	Repetition of clinical or subclinical seizures in a newborn who has abnormal neurologic symptoms between seizures, and all of the following on EEG: 1. Generalized high-voltage paroxsysmal discharges, *and* 2. Two or more discharges occurring every 10 s, *and* 3. These abnormalities persisting for at least 20 min
Scher	*(5)*	Continuous seizure activity for at least 30 min, or Recurrent seizures for greater than or equal to 50% of the recording time (of 1–3 h)
Wertheim	*(17)*	Continuous EEG seizure-type activity in one or more channels for at least 4 h, or separated for only a short period by activity consisting of frequent sharp waves or spikes
Ortibus	*(18)*	Total seizure duration greater than 30 min, *or* The sum of duration of seizures and/or periodic discharges is greater than 50% of the EEG recording

14.2 min *(16)*. Preterm infants, on the other hand, had an average seizure duration of only 3.1 min. The maximum duration was 16.3 min in a preterm and 159 min in a full-term infant. Thus, if a strict temporal criterion of 30 min is used to define NSE, very few newborns satisfy that criterion.

A recent trend in defining SE in older children and adults has been the use of progressively shorter temporal criteria. In 1999, Lowenstein, Bleck, and Macdonald proposed an "operational" definition of SE for older children and adults as 5 min or more of continuous seizures or "two or more discrete seizures between which there is incomplete recovery of consciousness" *(24)*. A separate "mechanistic" definition was also presented, describing SE as "a condition in which there is a failure of the 'normal' factors that serve to terminate a 'typical' generalized tonic-clonic seizure." Use of the operational definition in older children and adults can be justified by several factors. First, most secondarily generalized seizures in adults end within 2 min, so seizures persisting beyond that time are outside the expected duration *(25)*. Second, once a seizure lasts for 5 to 10 min, it is less likely to resolve spontaneously *(26)*. It also becomes more difficult to treat. In a lithium-pilocarpine model of induced seizures in rats, seizures lasting 45 min were less responsive to diazepam than those lasting 10 min *(27)*, i.e., seizures become increasingly refractory to treatment the longer they continue. If they continue, there is risk of neuronal injury. Meldrum and Brierley demonstrated that seizures persisting longer than 82 min led to brain damage in unanesthesized baboons *(28)*. In human adults, retrospective studies provide evidence for brain injury resulting from prolonged seizures *(29)*. The potential for neuronal injury following prolonged seizures provides justification for

assigning a short temporal standard in defining and treating SE. An operational definition for SE of 5 min allows the clinician to diagnose and treat SE before it becomes refractory to therapy.

The same approach and rationale used for a 5-min operational definition of SE in adults applies well to newborns. Given the potential for permanent neurologic sequelae in NSE *(30,31)*, earlier aggressive therapy is justifiable. Moreover, the operational definition of SE pulls together NSE with that in older age groups and finds common ground in an area where few other similarities exist.

3. ETIOLOGY

The causes of NSE mirror the causes of neonatal seizures in general (Table 3). The incidence of specific etiologies differs among various studies. Hypoxic-ischemic injury is the most common cause, accounting for as many as 50% of all neonatal seizures *(32)*. Infection is also frequent and is responsible for up to 25% of all cases *(32)*. Intracranial hemorrhage is less common in full-term infants but common in preterm newborns *(5)*. Congenital malformations are an infrequent cause, present in only 4.2% *(32)*. In the recent series of Mizrahi and Kellaway, the most common cause was hypoxic-ischemic encephalopathy (32%), followed by intracranial hemorrhage (17%), CNS infection (14%), infarction (7%), metabolic abnormalities (6%), inborn errors of metabolism (3%), and unknown (10%) *(33)*.

Metabolic derangements, especially hypoglycemia, hyponatremia, hypocalcemia, hypomagnesemia, or hypophosphatemia, must be recognized early because they require specific therapy directed at the primary abnormality. Mizrahi and Kellaway reported a 6% incidence of metabolic abnormalities *(33)*, whereas Sood and colleagues reported biochemical abnormalities in 29 of 59 neonates with seizures; these abnormalities were considered primary in 10 (17%), and secondary in 19 (to hypoxic-ischemic encephalopathy in 11) *(34)*. Hypocalcemia and hypoglycemia are the most important, with each accounting for approx 3% of neonatal seizures *(1)*. Hypocalcemia results in focal or multifocal clonic activity *(35)*. It has two major peaks in incidence. The early peak occurs in the first 2 to 3 d of life *(1)*. Most patients with early hypocalcemia are normal at follow-up *(35)*. Hypoglycemia, on the other hand, is more likely to result in permanent neurologic sequelae. The parietal and occipital regions are particularly susceptible *(36)*. Neonatal hypoglycemia demands aggressive treatment with intravenous glucose to avoid such injury. Onset is usually in the second day of life *(1)*. It is a misconception that seizures associated with metabolic abnormalities do not respond to antiepileptic drugs (AEDs).

It is important to distinguish neonatal seizures from neonatal-onset epilepsies *(37)*. Neonatal seizures may be caused by a specific disorder, such as infection, that require a specific therapy, whereas neonatal-onset epilepsies often have a genetic origin and are not caused by an acquired disorder. Both benign and malignant neonatal-onset epilepsy syndromes exist. Two important malignant syndromes in neonates are early myoclonic encephalopathy and early infantile epileptic encephalopathy. Two common benign syndromes are benign familial neonatal convulsions and benign idiopathic neonatal convulsions.

Table 3
Causes of Neonatal Seizures

Hypoxic-ischemic insult
Cerebrovascular disease (stroke)
Hemorrhage
Intraparenchymal
Intraventricular
Subarachnoid
Infection
Meningitis
Encephalitis
Sepsis
Metabolic
Hypoglycemia
Hypocalcemia
Hypomagnesemia
Hyperbilirubinemia
Narcotic withdrawal
Trauma
Brain malformations
Benign neonatal seizure syndromes
Benign familial neonatal convulsions
Benign idiopathic neonatal convulsions
Malignant syndromes
Early myoclonic encephalopathy (neonatal myoclonic encephalopathy)
Early infantile myoclonic encephalopathy
Inborn errors of metabolism

Early myoclonic encephalopathy (EME) begins in the first month of life and is characterized by erratic myoclonic jerks and encephalopathy *(38)*. It is also known as neonatal myoclonic encephalopathy. Tonic seizures and infantile spasms may also develop. The infants have severely delayed milestones, symmetric hypotonia, and cerebral atrophy, with progressive microcephaly. EEG shows a suppression-burst pattern that may evolve into hypsarrythmia. In most cases, the etiology is not found, although familial cases due to glycine encephalopathy, propionic acidemia, and methylmalonic acidemia have been reported.

Early infantile epileptic encephalopathy (EIEE) is also known as Ohtahara syndrome. The onset is before 3 mo of age and may be within the first several weeks, typically with tonic seizures (spasms) and suppression-bursts on EEG. It may evolve into infantile spasms *(38)*. The prognosis is similar to that of EME.

Benign familial neonatal convulsions (BFNC) is an autosomal dominant disorder with an 85% penetrance. Two gene loci have been linked to this disorder: BFNC 1 localizes to chromosome 20q13.3, and BFNC 2 localizes to chromosome 8q24. Seizures begin by the third day of life. Clonic (focal and multifocal) and tonic (focal and generalized) seizures predominate *(39)*, but myoclonic seizures can also be seen. The seizures are generally brief but may occur many times daily *(39)*. Ictal EEG recordings

Table 4
Inborn Errors of Metabolism Associated With Neonatal Seizures

Pyridoxine (Vitamin B6) dependency
Folinic acid responsive seizures
Nonketotic hyperglycinemia (NKH)
Sulfite oxidase deficiency, and molybdenum cofactor deficiency (combined deficiency)
Carbohydrate deficient glycoprotein disorder
Lactic acid disorders
Mitochondrial disorders
Maple syrup urine disease (MSUD)
Isovaleric acidemia (sweaty feet, cheesy odor)
3-methylcrotonyl-CoA carboxylase deficiency
Propionic acidemia
Mevalonic aciduria
Urea cycle defects
Hyperornithinemia-hyperammonemia-homocitrullinuria (HHH) syndrome
Neonatal glutaric aciduria type II
Biotin deficiencies, holocarboxylase synthetase deficiency
Fructose 1,6-diphosphatase deficiency
Hereditary fructose intolerance
Menkes disease (trichopoliodystrophy)
Peroxisomal disorders

Adapted from ref. *58*.

demonstrate a characteristic generalized attenuation of the background activity *(40)*. Interictally, the infants appear normal. The interictal EEG is also normal, allowing for distinction from more serious etiologies. In most cases, the seizures will resolve spontaneously, but 10 to 15% of patients may develop subsequent epilepsy *(38)*.

Benign idiopathic neonatal convulsions (BINC), or "fifth-day fits," occur in full-term, healthy newborns who have a seizure-free interval between birth and the onset of the seizures. The first seizure occurs between the fourth and sixth day in 80% of cases *(41)*. Seizures are clonic (focal or multifocal) or subtle—for example, apnea—and rarely occur after the neonatal period. Approximately 82% of patients will develop SE *(39)*. The interictal EEG often shows background abnormalities (discontinuous, asynchronous, or unreactive), but all other evaluations are normal. Outcome is generally excellent *(39,41)*.

Inborn errors of metabolism are an important cause of neonatal seizures (Table 4). Basic metabolic disorders (such as hypoglycemia or hypocalcemia) differ from inborn errors of metabolism (IEMs), which are usually genetic and need specific dietary or cofactor therapy. They should be suspected in the absence of an acute insult or structural cause, when seizures are accompanied by encephalopathy, and when seizures are refractory to standard AEDs. In a survey from British Columbia, the minimum incidence of IEMs is approx 40 cases per 100,000 live births *(42)*, but the incidence may be higher in certain settings. Chiaratti de Oliveira and colleagues found a 3% incidence anong 101 neonates admitted with hypoglycemia, metabolic

acidosis, jaundice, difficulty gaining weight, diarrhea, vomiting, hepatomegaly, splenomegaly, cataracts, apnea, convulsions, or abnormalities in tone *(43)*.

A full review of these disorders is beyond the scope of this chapter, but two deserve special attention because they are easily missed if not specifically considered: pyridoxine-dependent seizures and folinic-acid-responsive seizures. Pyridoxine-dependent seizures are rare *(44)*. They are recessively inherited and typically have their onset between birth and 3 mo of age *(38)*. EEG findings are nonspecific *(38)*. An intravenous (iv) pyridoxine test (50 to 100 mg iv) will typically result in resolution of epileptiform activity and cessation of seizures. Many patients with pyridoxine-dependent seizures are seizure-free with pyridoxine supplementation alone, but some develop mental retardation, sometimes with accompanying leukodystrophy *(45)*. Folinic-acid-responsive seizures are a newly described condition for which the pathophysiology is not fully known *(46)*. They begin in the first days of life and are refractory to AEDs and pyridoxine *(47)*. Folinic-acid-responsive seizures are diagnosed by neurotransmitter studies of cerebrospinal fluid (CSF), obtained from a lumbar puncture, which identify an abnormal peak (specific compounds not yet identified) suggestive of a defect in the folic acid pathway. Once neurotransmitter studies are obtained, folinic acid may be started, at 2.5 mg BID (up to 4 mg/kg/d). Seizures typically abate within 24 h of starting folinic acid *(47,48)*. White-matter changes have been reported in this condition *(47,48)*, and global developmental delays result *(47)*.

4. EVALUATION

The evaluation of neonatal seizures begins with a complete history and examination *(1)*. Next, the evaluation should focus on disease entities that require immediate treatment—hypoglycemia and bacterial meningitis. Blood glucose should be obtained and, if low, treated immediately. A lumbar puncture will not only aid in the diagnosis of meningitis, but will also help exclude less common disorders such as glucose transporter defect (with a CSF-to-plasma glucose ratio less than 0.35), mitochondropathy (with elevated CSF lactate), and glycine encephalopathy (with a CSF-to-plasma glycine ratio greater than 0.08) *(49)*. Serum chemistry studies should include sodium, potassium, calcium, magnesium, and phosphorus.

Neuroimaging should be performed. The study chosen will depend on the clinical status of the patient. In a critically ill preterm infant, cranial ultrasound is often preferable because it can be done at the bedside. Computed tomography (CT) has its greatest utility in diagnosing intracranial hemorrhage, but magnetic resonance imaging (MRI) is best for evaluating parenchymal lesions such as stroke or hypoxic-ischemic injury. Although neuroimaging aids in determining prognosis, its predictive value is inconsistent.

The EEG has particular utility in neonatal seizures. It helps determine the underlying cause, measures the degree of encephalopathy, and estimates prognosis. The greatest value of EEG is its ability to diagnose subtle and subclinical seizures. Unlike older children and adults, neonates frequently have electrographic seizures without a clinical accompaniment. Conversely, there are clinical seizures without accompanying electrographic changes *(4,5)*. Uncoupling of clinical events from the EEG is more

common in preterm infants *(5)*. For this reason, the interictal pattern plays an important role in diagnosing neonatal seizures. Interictal EEG abnormalities that are commonly associated with seizures include abnormalities of the background activity (e.g., voltage suppression or suppression-burst pattern) and excessive sharp transients, particularly if they occur in brief runs or are seen in a nonrandom distribution *(19)*. As discussed later, the EEG background activity correlates closely with outcome.

5. TREATMENT

Clear treatment guidelines do not exist for NSE, partly because the evolving concepts and criteria for NSE (i.e., its nebulous nature) have precluded comparing specific treatment regimens. Treatment decisions for NSE are generally extrapolated from what is known from neonatal seizure treatment (Table 5). Note that one key difference in the treatment of NSE vs SE in older age groups is the order of medication administration. In neonates, phenobarbital is considered the first-line AED, and benzodiazepines are used as either a second-or a third-line medication. At other ages, benzodiazepines, especially lorazepam, are often first-line agents *(50)*. In an adult study, lorazepam had the lowest infusion time *(22)*.

Phenobarbital is the most commonly used initial AED for neonatal seizures *(51)*, but it is effective as monotherapy in only one third of newborns *(52–54)*. The typical loading dose is 20 mg/kg. If the initial loading dose fails, this can be followed by sequential doses of 5 to 10 mg/kg to a maximum total dose of 40 mg/kg. The efficacy of a 40 mg/kg load is as high as 70% *(1)*. Doses beyond 40 mg/kg generally do not offer additional anticonvulsant effect and predispose the infant to excessive sedation. Phenobarbital has the advantage of predictable blood levels and can be converted easily to an oral form once the infant is capable of taking medications by mouth.

If 40 mg/kg of phenobarbital fails to control seizures, fosphenytoin/phenytoin is generally the next agent used. When given after an infant had already received a therapeutic dose of phenobarbital (with a serum level of 25 μg/mL), phenytoin was effective in an additional 24% of cases *(55)*. Fosphenytoin is preferable to phenytoin because its greater water solubility and neutral pH render it safer in the event of venous infiltration or intramuscular injection. The typical loading dose is 20 mg/kg of "phenytoin equivalents" (PE).

Approximately 15% of newborns do not respond to phenobarbital or fosphenytoin. Benzodiazepines are commonly used next. Lorazepam, at a dose of 0.05 to 0.10 mg/kg, is an appropriate option. It often results in cessation of seizures within 5 min and remains effective for 6.5 h on average (range of 3 to 19 h) *(56,57)*. Its half-life in neonates is 40 h, roughly four times longer than that in adults and older children *(57)*. Side-effects are minimal, and no respiratory or cardiac compromise is usually observed *(56,57)*. Because lorazepam may achieve rapid seizure control, it is reasonable to consider it sooner for neonatal seizures.

If neonatal seizures continue, treatable causes, such as specific metabolic disorders, must be excluded and other therapies used *(58)*. Midazolam, given as a continuous infusion of 0.1 to 0.4 mg/kg/h, is effective rapidly, often without any adverse effects *(59)*. Seizures are generally controlled within 1 h of administration, but subclinical,

Table 5
Guidelines for Treatment of Neonatal Status Epilepticus

Prior to AED administration, check serum glucose.
If hypoglycemia is present, give glucose 10% solution, 2 mL/kg iv, then AEDs.
If no hypoglycemia, administer AEDs:
1) Phenobarbital 20 mg/kg iv.
If seizures continue:
Further phenobarbital doses of 5 to 10 mg/kg to a maximum total dose of 40 mg/kg.
If seizures continue:
2) Fosphenytoin 20 mg/kg PE iv (may consider lorazepam).
If seizures continue:
3) Lorazepam 0.05 to 0.1 mg/kg iv.
Consider continuous EEG monitoring.
If seizures continue:
Explore possibility of inborn errors of metabolism.
Administer iv pyridoxine 50–100 mg with EEG guidance.
If seizures continue:
Consider administration of folinic acid.

Additional laboratory investigations should be considered, depending on each individual case. These include serum calcium and magnesium, lumbar puncture (to exclude infection and measure CSF glucose), neuroimaging (MRI with magnetic resonance spectroscopy [MRS] and diffusion-weighted imaging [DWI] if available; preferable to CT and ultrasound).

If seizures resolve prior to use of benzodiazepine, and the patient is not in stupor or coma, a routine EEG may suffice. If patient is in stupor or coma, or if benzodiazepine is required, continuous EEG monitoring is preferable.

electrographic seizures may continue. The half-life of midazolam is much shorter than that of lorazepam, allowing for easier titration *(59)*. Midazolam is not used as commonly as lorazepam but is an appropriate alternative given its efficacy and lack of side effects. Diazepam is less favorable because of rapid brain clearance, risk of cardiopulmonary failure, and variability of the therapeutic dose *(1)*.

Clinical experience with valproic acid has been limited in neonates, in part because it could previously be given only by oral or rectal administration. Rectal valproate was effective in two cases of refractory neonatal seizures *(60)*. However, intravenous valproate is now available (Depacon, 100 mg/cc). Alfonso and colleagues used iv valproate in two neonates who had received phenobarbital and phenytoin *(61)*. In the first, a loading dose of 10 mg/kg resulted in a level of 41 μg/ml after 45 min, and 33 μg/mL after 3 h. In the second child, 25 mg/kg increased the level to 100 μg/mL after 45 min and 78 μg/mL after 3 h. Each 1 mg/kg of IV valproate increased the level by 4 μg/mL at 45 min and 3 μg/mL at 3 h. Hypotension occurred in an older child at an infusion rate of 30 mg/kg/hr (0.5 mg/kg/min) *(62)*. The maintenance dose is started at 20 mg/kg/d.

There is limited clinical experience in neonates with other AEDs. Carbamazepine was effective in a study of 10 neonates but is used sparingly *(63)* because it has no intravenous preparation. Lidocaine has had greater clinical use but has been associated with cardiac arrythmias and hypotension *(1)*. When seizures are refractory to standard AEDs, trials of pyridoxine and folinic acid are necessary, and other inborn errors of metabolism need to be considered.

6. OUTCOME

Few studies focus specifically on outcome in NSE, but follow-up data do exist for neonatal seizures in general. Etiology is the major determinant. Because etiologies differ, follow-up data also differ in preterm and full-term neonates. Neuroimaging findings, EEG results, physical exam abnormalities, and other clinical features are also factors determining outcome. Overall, neonatal seizures carry a substantial risk of morbidity and mortality. Although the exact rates vary from study to study, death or moderate to severe neurologic impairment develop in roughly half of all patients *(35,64,65)*. Possible sequelae include epilepsy, mental retardation, and focal neurologic dysfunction *(35)*. Reviewing the collective data from all patients is of limited usefulness, however, as the risks can be more accurately stratified by taking into account individual clinical features.

By far the most important variable in determining outcome is etiology. Seizures are often a symptom of an underlying neurologic insult, and the type and extent of that insult generally determine ultimate prognosis. This is especially so in the newborn, in whom "idiopathic" seizures are rare. Neonatal seizures resulting from hypoxic-ischemic injury can be fatal in as many as 50% of patients *(14)*, and a normal developmental outcome may occur in as few as 10% *(35)*. A poor outcome is particularly likely when seizures persist beyond the second day of life. When seizures occur on d 1 and 2 only, however, the outcome is more favorable *(32)*. Neonatal seizures may compound the injury from the original insult, so careful screening and aggressive treatment for seizures should take place in all newborns with hypoxic-ischemic encephalopathy *(66)*. Transient reversible insults, on the other hand, such as narcotic withdrawal or early hypocalcemia, portend a more favorable prognosis *(64)*.

The EEG reflects the severity of any neurologic insult, so it has utility in determining prognosis. Background activity is particularly important in this regard. Patients with unifocal, transient discharges, but normal background activity, commonly have relatively benign diseases such as subarachnoid hemorrhage or reversible metabolic disturbances *(35)*. On the other hand, severe generalized abnormalities, such as a suppression-burst pattern or an isoelectric EEG (electrocerebral inactivity), are more likely the result of serious pathology. Thus, of patients who are clinically normal at follow-up, most had normal or only mildly abnormal EEGs in the neonatal period *(35)*. In one study, no patient with normal or only mildly depressed EEGs died *(18)*. Conversely, a suppression-burst pattern or an isoelectric EEG were associated with death or severe neurologic abnormalities in 80 to 100% of patients *(18)*.

The interictal neurologic examination is equally important in predicting outcome. A normal exam strongly correlates with a normal outcome, and a severely abnormal exam portends an unfavorable prognosis *(18)*. Neuroimaging is less predictive, but global abnormalities do correlate with severe neurologic injury or death while focal abnormalities are more variable in their outcomes *(18)*.

The few studies that specifically address NSE have shown poor outcomes. Andre and colleagues reported normal outcomes in 38% of NSE patients, compared with 64% of those with brief, isolated seizures *(32)*. In another series of 15 patients with NSE, 4 died, all with hypoxic-ischemic injury *(14)*. Ortibus and colleagues

demonstrated an unfavorable prognosis in 86% of patients with NSE *(18)*. They found a correlation between the quantity of periodic discharges and severity of outcome: EEGs with a greater percentage of periodic discharges were associated with a worse prognosis. This association does not indicate a causal relationship of increased discharge frequency to neurologic injury, but the possibility that frequent discharges might contribute to neuronal injury supports aggressive treatment of NSE.

7. CONCLUSION

Although NSE shares few similarities with SE in older patients, both require a 5-min operational definition for prompt diagnosis and treatment. The clinical manifestations of NSE can be absent or subtle, so a high degree of clinical suspicion is required. Treatment should focus first on potentially injurious causes, such as hypoglycemia. The treatment approach is not standardized but should be extrapolated from experience with neonatal seizures in general. Failure to diagnose and treat the condition promptly may contribute to neurologic injury. Ultimately, the etiology, clinical exam, and EEG findings are the most important factors in determining prognosis.

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