Current Clinical Neurology
Series Editor: Daniel Tarsy

Frank W. Drislane
Peter W. Kaplan *Editors*

Status Epilepticus

A Clinical Perspective

Second Edition

Humana Press

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Daniel Tarsy, MD, Department of Neurology Beth Israel Deaconness Hospital Boston, MA USA

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Editors
Frank W. Drislane
Department of Neurology, Harvard Medical School, Comprehensive Epilepsy Center
Beth Israel Deaconess Medical Center
Boston, MA
USA

Peter W. Kaplan
Department of Neurology
Johns Hopkins Bayview Medical Center
Baltimore, MD
USA

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To our wives, Rosemarie Yevich (with Frank W. Drislane) and Nora Michele Frenkiel (with Peter W. Kaplan) who have been the source of unstinting support over very many years; they and our children (Catherine, Helen, and Edward Drislane, and Emma and Alex Kaplan) have tolerated generously the many hours beyond the work-day that we have devoted to our study of status epilepticus.

Series Editor's Introduction

This second edition of *Status Epilepticus: A Clinical Perspective* is being published 12 years after the first edition made its appearance in 2005. At that time the goal was to recognize and document the very rapid growth which had taken place in the field during the previous decade by comparison with a history of considerably slower progress prior to that time. Since then interest in "status" has continued to grow at an accelerating rate as indicated by the increase in the number of chapters in this volume from 17 to 29 and the number of contributing authors from 18 to 38. As stated by the editors, there has been an expanding appreciation of the wide variety of forms of status epilepticus (SE) with different pathophysiologies, a greater recognition of the increasing number of underlying medical and newly discovered neurological illnesses in which SE occurs, and the development of new treatments, both pharmacological and nonpharmacological, all of which justify a fresh overview of the subject.

New chapters in this volume include new and unusual causes of SE, SE as it presents in the generalized epilepsies, reviews of myoclonic, anoxic myoclonic, and tonic, clonic, and atonic forms of SE, new and evolving concepts of nonconvulsive SE, imaging in SE, expanded awareness of several new and unique cognitive manifestations of SE, increased availability of continuous EEG monitoring with recognition of several periodic electroencephalographic patterns in SE, persistent clinical consequences of both convulsive and nonconvulsive SE, SE in critically ill children, and a particularly important chapter on new and expanding clinical trial methodologies in treatment trials of SE. To create this volume the editors, Dr. Frank Drislane and Dr. Peter Kaplan, have collected as well as added an impressive number of new contributing authors with broad national and international representation.

Boston, MA, USA — Daniel Tarsy, MD

Preface

Status epilepticus is a wonderful field of study and of clinical work. Its tremendously 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 experimental and clinical cases is instructive about neuronal connections and helps to explain brain function in illness and in health.

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 for serious illness.

Status epilepticus was recognized in antiquity but only became the subject of medical writings in the late nineteenth century and of informative laboratory studies in the last 50 years. The existence of nonconvulsive status was posited by Charcot but only became clearly diagnosable after Berger developed the EEG in the mid twentieth century. In Shorvon's 1994 monograph, *Status Epilepticus: Its Clinical Features and Treatment in Children and Adults,* he lamented the fact that there were just 370 publications related to status in his review of a large database through 1978. Now, there are several hundred helpful papers on status every year.

The great clinical neurophysiologist Niedermeyer said of epilepsy, "There is no disease named 'epilepsy.'" Rather, there are very many illnesses that cause epileptic seizures. Similarly, over the last few decades, neurologists have learned to ask "Which type of status?" when asked how to treat it. This book emphasizes the recognition and diagnosis of the very many different forms of status epilepticus and the necessarily different evaluation, management, and treatment of each. Here, those types are organized into status with convulsions or major abnormal movements (Chaps. 7–18) and those considered nonconvulsive (Chaps. 19–25).

There has been a dramatic increase in useful knowledge about the treatment of convulsive status since the previous edition of this book, discussed in several chapters (especially Chaps. 16–18, and 29). There has been a similar growth in recognition of the remarkably varied forms of nonconvulsive status, the huge range of underlying illnesses that can cause both convulsive and nonconvulsive status (e.g. several autoantibody syndromes), and also of entirely new and different types of treatment, whether dietary, new drugs, or stimulation. The field has become much more complicated, but better understanding of these complex illnesses and new insights and approaches to them may help to achieve the goal of better treatment for patients with this often very threatening illness.

Of necessity, discussion of these many types of status epilepticus and many old and new treatments will occasion some overlap or duplication among chapters. Those on status in the very young (Chaps. 26–28) offer an illustration. One focuses on the youngest patients (neonates), another on unusual status syndromes in children, and the third on the most difficult cases of refractory status in pediatric ICUs. The chapters overlap, particularly when discussing

medications, but it should be apparent that these are different areas of expertise. In all chapters, different approaches, controversies, and speculation were not proscribed, but rather encouraged. Indeed, different perspectives and opinions are worth considering, as many can be educational. Different chapters may offer different approaches to the same problem, but in the end, we are confident that most of our authors would have very similar approaches to similar cases, and also that seeing different styles and then making an independent decision is a good way of refining one's own approach to the management of status epilepticus.

While this volume focuses on a clinical perspective, all neurologists confronting status epilepticus will want to understand better its underlying biology and pathophysiology. Information on basic studies appears in many chapters, but especially in those dealing with the clinical and pathologic consequences of generalized convulsive status on the one hand and nonconvulsive status on the other (Chaps. 9, 10, and 25).

Over the last decade, the booming practice of continuous EEG monitoring, especially in critically ill patients, has changed the field, with better identification of status, while simultaneously generating controversies about what is and what is not status epilepticus (see Chaps. 19 and 23).

One of the advantages and pleasures of working in a field of academic Neurology over decades is the opportunity to meet and work with individuals in the enlarging international community of scholars interested in status epilepticus, many of whom have given generously of their time and wisdom to this volume. We owe a tremendous debt of gratitude to our many wonderful co-authors on this project—whom we believe to be among the finest neurologists, epileptologists, and clinical neurophysiologists in the world. The range of their expertise and ability to inform us is impressive, and the range of their backgrounds similarly diverse, with their homes in at least a dozen countries. Much of what we know about status epilepticus has come from reading their papers, listening to their lectures, and discussing status epilepticus at national and international meetings or other conferences, and in the hallways and conference rooms of our home institutions, or theirs. In reviewing their contributions here, we have enjoyed learning even more.

It is important and a pleasure to thank our editors at Springer, Mr. Greg Sutorius, senior editor, for initiating the 2nd edition and helping to shepherd it through, and developmental editor, Ms. Katherine Kreilkamp, for offering help with far more than customary production editing—everything from assistance with permissions to guidance on formatting and even syntax, with mastery of the process, gracious author communication and encouragement to finish, and shockingly rapid responses to our queries.

Some of our best experiences in Medicine have been in helping get an individual patient through the threatening illness of status epilepticus, and especially in the most refractory cases. We remember the successes gladly, and we remember the failures very sadly, and we hope that the wisdom of our co-authors will help increase the number of successes for our readers and their patients.

Boston, USA
Baltimore, USA
February 2017

Frank W. Drislane
Peter W. Kaplan

Contents

Contributors

Nicholas S. Abend Division of Neurology, Departments of Neurology and Pediatrics, The Childrens Hospital of Philadelphia, The University of Pennsylvania, Philadelphia, PA, USA

Vincent Alvarez Service de Neurologie, CHUV (Centre Hospitalier Universitaire Vaudois), Lausanne, Switzerland

Gerhard Bauer Department of Neurology, Medical University of Innsbruck, Innsbruck, Tyrol, Austria

Michael G. Benatar Department of Neurology, Neuromuscular Division, University of Miami, Miami, FL, USA

Leonardo Bonilha Department of Neurology, Clinical Neurophysiology Laboratories, Clinical Services, MUSC Comprehensive Epilepsy Center, The Medical University of South Carolina, Charleston, SC, USA

Mackenzie C. Cervenka Department of Neurology, The Johns Hopkins Hospital, Baltimore, MD, USA

Bernard S. Chang Comprehensive Epilepsy Center, Harvard Medical School, Beth Israel Deaconess Medical Center, Boston, MA, USA

Monica B. Dhakar Department of Neurology, Yale University School of Medicine, New Haven, CT, USA

Tolga D. Dittrich Unviersity Hospital Basel, Basel, Switzerland

Frank W. Drislane Department of Neurology, Harvard Medical School, Beth Israel Deaconess Medical Center, Neurology, Boston, MA, USA

Barbara A. Dworetzky Department of Neurology, Brigham and Womens Hospital, Harvard Medical School, Boston, MA, USA

Jonathan C. Edwards Department of Neurology, Clinical Neurophysiology Laboratories, Clinical Services, MUSC Comprehensive Epilepsy Center, The Medical University of South Carolina, Charleston, SC, USA

Brandon Foreman Department of Neurology & Rehabilitation Medicine, Division of Neurocritical Care, University of Cincinnati Medical Center, Cincinnati, OH, USA

Nathan B. Fountain Department of Neurology, University of Virginia, Charlottesville, VA, USA

Nicolas Gaspard Service de Neurologie et Centre de Référence pour la Prise en Charge de l'Epilepsie Réfractaire, Université Libre de Bruxelles – Hôpital Erasme, Brussels, Belgium; Neurology Department and Comprehensive Epilepsy Center, Yale University School of Medicine, New Haven, CT, USA

Elizabeth E. Gerard Department of Neurology, Feinberg School of Medicine, Northwestern University, Chicago, IL, USA

Diana M. Gomez-Hassan Department of Radiology, University of Michigan Hospitals, Ann Arbor, MI, USA

Howard P. Goodkin Departments of Neurology and Pediatrics, University of Virginia, Charlottesville, VA, USA

Jonah Grossman Department of Neurology & Rehabilitation Medicine, Division of Neurocritical Care, University of Cincinnati Medical Center, Cincinnati, OH, USA

Réjean M. Guerriero Neurology, Division of Pediatric and Developmental Neurology, Washington University School of Medicine and St. Louis Childrens Hospital, St. Louis, MO, USA

Cecil D. Hahn Division of Neurology, The Hospital for Sick Children, Toronto, ON, Canada

Hiba A. Haider Division of Epilepsy, Emory University School of Medicine, Atlanta, GA, USA

Abeer J. Hani Department of Pediatrics and Neurology, Gilbert and Rose-Marie Chagoury School of Medicine, Lebanese American University, Chouran, Beirut, Lebanon

Lawrence J. Hirsch Department of Neurology, Yale University School of Medicine, New Haven, CT, USA

Sara Hocker Division of Critical Care Neurology, Department of Neurology, Mayo Clinic, Rochester, MN, USA

Aatif M. Husain Department of Neurology, Duke University Medical Center, Durham, NC, USA; Neurodiagnostic Center, Veterans Affairs Medical Center, Durham, NC, USA

Suchitra Joshi Department of Neurology, University of Virginia, Charlottesville, VA, USA

Peter W. Kaplan Department of Neurology, Johns Hopkins Bayview Medical Center, Baltimore, MD, USA

Lisa Knopf Comprehensive Epilepsy Center, Harvard Medical School, Beth Israel Deaconess Medical Center, Boston, MA, USA

Christian M. Korff Pediatric Neurology Unit, University Hospitals of Geneva, Geneva 14, Switzerland

Michail Koutroumanidis Department of Clinical Neurophysiology and Epilepsies, St Thomas' Hospital, Guy's & St Thomas' NHS Foundation Trust, London, UK

Vaishnav Krishnan Department of Neurology, Harvard Medical School, Beth Israel Deaconess Medical Center, Neurology, Boston, MA, USA

Mary Kurian Pediatric Neurology Unit, University Hospitals of Geneva, Geneva 14, Switzerland

Suzette M. LaRoche Department of Neurology, Mission Health System, Emory University School of Medicine, Asheville, NC, USA

Jong Woo Lee Department of Neurology, Brigham and Womens Hospital, Boston, MA, USA

Tobias Loddenkemper Neurology, Division of Pediatric and Developmental Neurology, Washington University School of Medicine and St. Louis Childrens Hospital, St. Louis, MO, USA

Emily L. McGinnis Division of Neurology, Departments of Neurology and Pediatrics, The Childrens Hospital of Philadelphia, The University of Pennsylvania, Philadelphia, PA, USA

Aidan Neligan Institute of Neurology, National Hospital for Neurology and Neurosurgery, University College London, London, UK

Karthik Rajasekaran Neurology & Neurotherapeutics, University of Texas Southwestern Medical Center, Dallas, TX, USA

James J. Riviello Departments of Pediatrics and Neurology, Sections of Pediatric Neurology, Epilepsy, Clinical Neurophysiology, Neurocritical Care, and Developmental Neuroscience, Texas Childrens Hospital, Baylor College of Medicine, Houston, TX, USA

Andrea O. Rossetti Service de Neurologie, CHUV (Centre Hospitalier Universitaire Vaudois), Lausanne, Switzerland

Stephan U. Schuele Department of Neurology, Feinberg School of Medicine, Northwestern University, Chicago, IL, USA

Anna Serafini Department of Neurology, Feinberg School of Medicine, Northwestern University, Chicago, IL, USA

Douglas M. Smith Division of Neurology, Departments of Neurology and Pediatrics, The Childrens Hospital of Philadelphia, The University of Pennsylvania, Philadelphia, PA, USA

Raoul Sutter Department of Neurology and Intensive Care Medicine, Unviersity Hospital Basel, Basel, Switzerland

Benjamin Tolchin Department of Neurology, Brigham and Womens Hospital, Harvard Medical School, Boston, MA, USA

Eugen Trinka Department of Neurology, Christian Doppler Medical Centre, Paracelsus Medical University, Centre for Cognitive Neuroscience, Salzburg, Austria

Iris Unterberger Department of Neurology, Medical University of Innsbruck, Innsbruck, Tyrol, Austria

Matthew C. Walker Institute of Neurology, National Hospital for Neurology and Neurosurgery, University College London, London, UK

Diana J. Walleigh Division of Neurology, Departments of Neurology and Pediatrics, The Childrens Hospital of Philadelphia, The University of Pennsylvania, Philadelphia, PA, USA

Elizabeth J. Waterhouse Department of Neurology, Virginia Commonwealth University School of Medicine, Richmond, VA, USA

Part I
Overview

History of Status Epilepticus

1

Peter W. Kaplan and Eugen Trinka

From Antiquity to the Nineteenth Century

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], 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 629–539 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 in England noted (in *Pathologiae cerebri et nervosi generis specimen. In quo agitur de morbis convulsivis et de scrobuto*, 1667, Pordage S, translator, 1681.) [4]:

> [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.

P.W. Kaplan (✉)
Department of Neurology, Johns Hopkins Bayview Medical Center, 4940 Eastern Avenue, 301 Building, Room 2115, Baltimore, MD 21224, USA
e-mail: pkaplan@jhmi.edu

E. Trinka
Department of Neurology, Christian Doppler Klinik Salzburg, Paracelsus Medical University, Ignaz Harrer Straße 79, 5020 Salzburg, Austria
e-mail: e.trinka@salk.ateugen@trinka.at

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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 eighteenth and early nineteenth 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 [4, 6]. 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, 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 malades 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 [4, 6].

Status Epilepticus Within the Greater Context of Epilepsy

The use in English of status epilepticus, however, finally appeared when Bazire translated Armand Trousseau's *Lectures in Clinical Medicine* [4, 7]. 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 [4, 6]. 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," [4] with its own particular characteristics, albeit confined to tonic-clonic seizures.

Temkin's footnote on Hunter states: "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" [4, 5].

In Britain, cases of status epilepticus were described by Gowers, Ferrier, Jackson, Horsley, Turner, Sieveking, and Coleman [4]. 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 [4].

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 [4, 7].

Bourneville confined the term *état de mal* to convulsive status only. Nevertheless, nonconvulsive forms of status epilepticus had also been described already by the end of the nineteenth century. The first historical case of absence status seems to be documented on an *ex-voto* table of 1501 in the parish church of Gmünd in Austria [8]. Bright in 1831 [9] and Charcot in 1888 [10] described 'epileptic fugue.' West accurately described infantile spasms in 1841 [11]. Jackson [12] and Gowers [13] described febrile status, postictal confusion, and myoclonic status. Finally, with Kojewnikoff's description of *epilepsia partialis continua* in 1895 [14] all forms of convulsive and nonconvulsive status had been elaborated on in some detail. Otto Binswanger in 1898 gave a detailed account on the pattern of seizure recurrence and on status epilepticus in his monograph on epilepsy [15]. He distinguished single attacks, repetitive seizures, and serial seizures which could lead to status epilepticus, where intervals between the attacks were no longer discernable. Without giving a time estimate, he reported that the postictal disturbances were more severe if the intervals between the seizures were shorter.

The First Case Series—Clark and Prout

Writing in 1903, Pierce Clark and Thomas Prout described the pathological and classical clinical appearances of status epilepticus in 38 patients [16]. 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 days associated with changes in reflexes, pupil responses, and lateral and upward eye movement, eventually leading to clamminess of the skin, bodily wasting, and bedsores, and finally, a stuporous stage which often ended fatally—descriptions all remarkable in their detail and precision [16]. Clark and Prout also recognized a 'heralding' form of status, which was first mentioned in Calmeil's doctoral thesis in 1824 ("*Il y'a des cas où un accès à peine fini, un autre recommence, et successivement coup sur coup, si bien qu'on peut compter quarante, soixante accès sans interruption*") ("There are cases in which—the seizure having barely ended—another starts, and [continues] successively blow after blow, to the extent that they may number forty, sixty seizures without a break") and by Obersteiner 1873 [17], who published the first work in German.

Even as the apparently striking features of convulsive status epilepticus were overlooked until relatively recently, 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 built later 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. 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 [18]:

> [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 [18]:

> 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 [19], 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.

Nonconvulsive states of automatism received the attention of Jules Falret (1824–1902) who referred to them as "*petit mal intellectuel*" [20]. "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" [20].

Höring [21], 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.

Status Epilepticus as the "Maximum Expression of Epilepsy"

In the late 1800s Charcot, in Paris, believed that somnambulistic states derived from ongoing ictal (epileptic) conditions. To press his point, he presented a patient in his "*Leçons du mardi*" at the Saltpêtrière Hospital in Paris [22] (Fig. 1.1). This 37-year-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 [22]. In Britain, Gowers, in his work *Epilepsy* [13], 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 further [13], refers to the studies of Bourneville and provides one clinical description, noting:

> 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 violent 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 lessen, 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 patients have recovered [13, p. 193–4].

While addressing treatment, Gowers [23] 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 [13, p. 273].

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 [13, p. 290–1].

Thus long neglected in the written records of medicine, it would seem that status epilepticus had 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

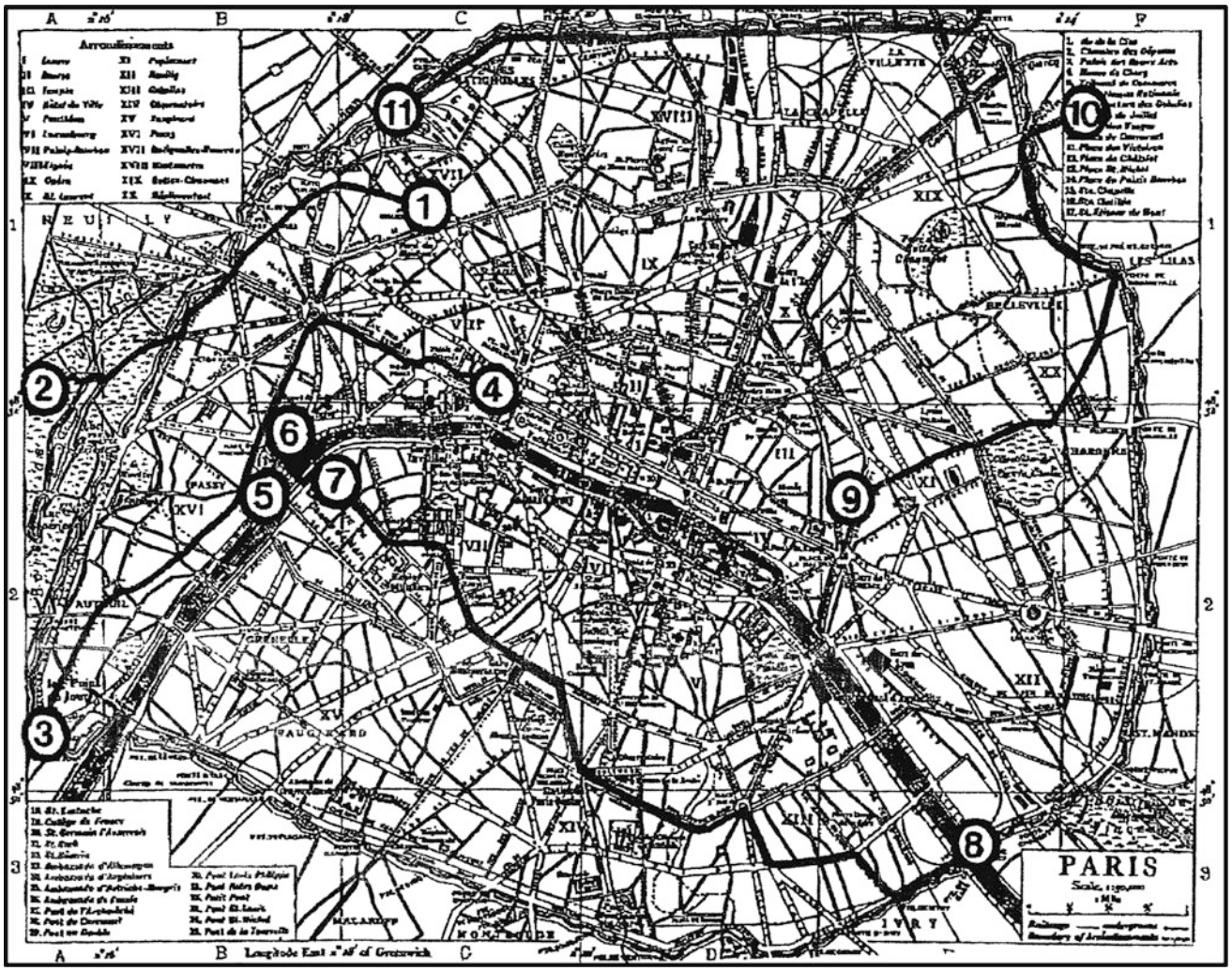

Fig. 1.1 Map of Paris in the 1880s showing the peregrinations taken by a mailman with bromide-responsive epileptic "wanderings"—an early case of nonconvulsive status epilepticus? (From Shorvon [4], with permission)

correlation led to its identification as the "maximum expression of epilepsy" [4].

The Advent of Electroencephalography

After 1924 when Hans Berger discovered the recordable electrical impulses from the brain using electroencephalography (EEG), there was a concerted effort to link the now-measurable brain dysfunction with its clinical correlates, and the study of epilepsy was rapidly transformed into a technically driven clinical science for the 50 years that followed. (More recently, neuroimaging, especially MRI, appears to have taken over a part of this role.) Berger was the first to systematically study patients with epilepsy using EEG. In his seventh report in 1933, he recorded the first EEG of focal motor seizures in a patient with *epilepsia partialis continua*, and recorded another patient with 3/sec spike and wave discharges [23]. Following this, a series of single case reports and series used a different terminology (e.g. *epilepsia minor continua, status pyknolepticus, absence continua,* absence status spike-wave stupor, and others). It soon became clear that not every patient with a milder form of status had generalized spike-wave discharges [24]. The influence of EEG on scientific thought was so dominant that etiologic and pathological research dawning in the nineteenth century almost stopped completely. In Germany, the Nazi regime and the Second World War took its toll, and many of the researchers in this field had to leave their countries.

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. Gibbs, Gibbs, and Lennox regarded a seizure as a "paroxysmal cerebral dysrhythmia" [25], and in 1945 Lennox

described the clinical and EEG features of absence status in his cousin Ann Lennox and coined the term *petit mal status* [26]. This was followed in 1956 by Gastaut and Roger, who described a nurse with complex partial status epilepticus (CPSE) that may have lasted several months. They called the condition *état de mal temporal* [24].

From about the 1950s onwards, a somewhat more detailed investigation of the consequences of SE came with the publication of case series of SE. Whitty and Taylor noted that a longer duration of SE appeared to correlate with a worse outcome [27], with 1/3 of their patients dying. It was Janz in 1953 who systematically studied the relationship of the number of grand mal seizures and the average interval between the seizures preceding status epilepticus [28]. Based on the analysis of 103 grand mal seizures he found that 3 or 4 more seizures would follow when the inter-seizure interval dropped to 2–6 h. If the inter-seizure interval were <1 h at least 6 seizures, and most likely "true" status epilepticus, would ensue if seizures were not terminated by treatment. In the 42 cases of SE reported by Janz in 1964, those that were symptomatic were found to have a frontal origin [29]. In general, symptomatic SE was commoner than idiopathic types. Hunter's review of the Register General in the United Kingdom reported that SE accounted for a third of the cases of death in patients with epilepsy [5]. About 25% of status seen at Queen Square was thought to be precipitated by changes in medication, with some 30% associated with an inter-current infection.

The Modern Era

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 [30] (see also Chap. 2, "Types of Status Epilepticus: Definitions and Classification"). Since the 1960s, greater attention turned to the physiologic underpinnings, neurochemistry, and pharmacology of status epilepticus, most recently with functional imaging techniques.

Regarding the therapy of status epilepticus, phenytoin began to replace bromides and phenobarbital as the mainstay of repetitive seizure or SE treatment in the United States. By 1968 an intravenous dose of 1000 mg was advocated, and reported to have been immediately effective in 18 of 31 patients [31]. Case series included treatment with lidocaine or paraldehyde [32], and phenobarbital and anesthetics were also used. The major advance was the use of parenteral benzodiazepines, including diazepam and lorazepam (and clonazepam in Europe). More recently, the delineation of refractory and super-refractory cases of SE, often in ICU patients, brought about the use of different anesthetic agents such as propofol, pentobarbital, and midazolam. There is now an emerging literature on infectious and autoimmune causes (e.g. paraneoplastic limbic encephalitis) increasingly recognized in pharmaco-resistant and prolonged cases of SE. With increasing numbers of patients supported in cardiac intensive care units and the advent of temperature directed post-cardiac arrest management, post-anoxic SE is being diagnosed and managed increasingly, albeit often with little benefit. Cases arising after respiratory arrest without cardiac arrest appear sometimes to do better. With various treatment regimens moving beyond first, second, and third-line treatments, newer modalities such as the ketogenic diet, deep brain stimulation, and others are being explored (see also Chap. 18, "Treatment of Refractory and Super-Refractory Status Epilepticus"), and their history remains to be written.

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Types of Status Epilepticus: Definitions and Classification

2

Eugen Trinka

Introduction

Status epilepticus (SE) is often referred to the "*maximum expression of epilepsy.*" It is also a very severe expression of an acute brain insult or systemic disturbance leading to excessive hyperexcitation of nervous tissue. But what is status epilepticus? The definition and classification of SE is best understood in its historical context, which is covered extensively in Chap. 1, "History of Status Epilepticus."

The modern definition and classification of SE dates to the Xth Marseille Colloquium (the 10th European Electroencephalographic Meeting) in 1962, which was completely devoted to status epilepticus. Henri Gastaut, undoubtedly the dominant figure in epilepsy at the time, led the conference, held 2 years before he embarked on a seizure classification system. A total of 103 participants presented 237 cases with both clinical and EEG findings of abnormally prolonged or serially repeated seizures [1]. The proposed definition of SE was intended to be "*etymological*"—now referred to as *semantic* or *conceptual*—consistent with the meaning of the original term *status* in Latin: "*Status epilepticus is a term [used for] a seizure that persists for a sufficient length of time or is repeated frequently enough to produce a fixed and enduring condition.*" Although there was no duration specified in the definition, Gastaut later proposed 60 min as the defining minimum duration for SE. Though not explicitly stated in the Colloquium report, Gastaut recalled in 1983 that there was a specific hypothesis that there were as many types of status as there were types of epileptic seizures [2]. Gastaut, along with his colleagues at the time, was leading the classification of seizure types. SE was divided into partial, generalized, or unilateral types and basically mirrored the seizure classification [3]. In the 1981 revision, the definition was changed minimally into a "*seizure* [that] *persists for a sufficient length of time or is repeated frequently enough that recovery between attacks does not occur.*" Status was classified under the term "prolonged or repetitive seizures (SE)" and was divided into partial (e.g., Jacksonian) or generalized (e.g., absence status, or tonic–clonic status). "When very localized motor status occurs, it is referred to as *epilepsia partialis continua*" [4].

This loose definition, without further explanation of what "fixed and enduring" or "sufficient length" meant, as well as the lack of clinical descriptions (i.e., semiology) of the SE types, was an inherent weakness of the 1970 Classification and its 1981 revision—which was not improved by the proposed diagnostic scheme in 2001 in which SE was classified within the different seizure types [5], and also not in the report of the International League Against Epilepsy (ILAE) Core Group on Classification [6]. In the last ILAE report of 2006, SE was defined "*mechanistically*" ("conceptually" would have been a clearer term), as "*the failure of the natural homeostatic seizure-suppressing mechanisms responsible for seizure termination*" without mentioning a specific time frame for the duration [6].

New Definition and Classification of Status Epilepticus

The previously described concepts, while highly valuable, were imprecise as they did not define the duration of a seizure that was "fixed and enduring" or of "sufficient length," nor was there a clinical description (semiology) of the types of SE in the classification of 1970 (Table 2.1) or in its 1981 revision. In the report of the ILAE Core Group [6], the clinically used dichotomy of convulsive and nonconvulsive status was abandoned as "lay expressions" (Table 2.2). None of the aforementioned definitions guided clinicians in their treatment decisions or helped to improve outcomes by setting clear standards as to when emergency treatment should be started. In the past, experts suggested that 30 min

E. Trinka (✉)
Department of Neurology, Christian Doppler Medical Centre, Paracelsus Medical University, Centre for Cognitive Neuroscience, Ignaz Harrer Strasse 79, 5020 Salzburg, Austria
e-mail: e.trinka@salk.at; eugen@trinka.at

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Table 2.1 Clinical classification of status epilepticus per Gastaut 1970 [3]

Continuous seizure types
Generalized SE
Generalized tonic-clonic SE
Clonic SE
Absence SE
Tonic SE
Myoclonic SE
Focal SE
Epilepsia partialis continua
Aura continua
Limbic SE (psychomotor status)
Hemiconvulsive SE with hemiparesis

SE = status epilepticus

Table 2.2 Classification proposal from the 2006 Core Group of the Commission on Classification of the ILAE [6]

I. *Epilepsia partialis continua* of Kojevnikov
A. As occurs with Rasmussen syndrome B. As occurs with focal lesions C. As a component of inborn errors of metabolism
II. Supplementary motor area SE
III. *Aura continua*
IV. Dyscognitive focal (psychomotor, complex partial) SE
A. Mesial temporal B. Neocortical
V. Tonic-clonic SE
VI. Absence SE
A. Typical and atypical absence SE B. Myoclonic absence SE
VII. Myoclonic SE
VIII. Tonic SE
IX. Subtle SE

SE = status epilepticus

of ongoing seizure activity could be regarded as "fixed and enduring." Over the past two decades, the timelines in clinical trials and treatment recommendations were moved progressively to 20 min and then to 10 min. Lowenstein and colleagues suggested that a generalized tonic–clonic seizure longer than the usual 2–3 min is abnormally prolonged and should be treated as SE [7]. They recommended a time limit for convulsive status of 5 min. This concept opened the door to changing our view of the classical definition of SE.

The Commission of Classification and Terminology of the ILEA (Chair: Dr. Ingrid E. Scheffer) and the Commission on Epidemiology (Chairs: Drs. Ettore Beghi and Dale Hesdorffer) charged a Task Force, chaired by Dr. Daniel H. Lowenstein and Dr. Eugen Trinka, with clinical researchers and epidemiologists, to revise the classification of SE in 2009. Members were Dr. Hannah Cock (UK), Dr. Hesdorffer (USA), Dr. Lowenstein (USA), Dr. Andrea O. Rossetti (Switzerland), Dr. Scheffer (Australia), Dr. Shlomo Shinnar (USA), Dr. Simon Shorvon (UK), and Dr. Trinka (Austria). This group aimed to achieve a unifying definition and classification of SE serving all purposes [8]. Because current knowledge regarding the pathophysiology and underlying neurobiology of SE is far from complete, the Task Force recognized that a proposed definition should include two dimensions: first, a conceptual approach based on the scientific evidence, and second, an operational frame to guide management.

A classification refers to the way in which items are organized and should be based ideally on the underlying neurobiology to form natural classes or entities [9]. Again, knowledge of the different types of SE and its underlying mechanisms are, at best, marginal so any classification would be a compromise between a conceptual, scientific (drawing on what is known) classification and a pragmatic empirical classification [10]. The Task force issued the following definition: "*Status epilepticus is a condition resulting either from the failure of the mechanisms responsible for seizure termination or from the initiation of mechanisms, which lead to abnormally prolonged seizures (after time point t1). It is a condition, which can have long-term consequences (after time-point t2), including neuronal death, neuronal injury, and alteration of neuronal networks, depending on the type and duration of seizures*" [8].

There are two novel aspects included in this definition: First, conceptually, SE does not represent only a "failure of seizure suppressing mechanism," as maintained in 2006. Recent advances in the basic understanding of SE have made it clear that there is likely a multitude of simultaneous, parallel processes underlying SE, suggesting that initiation of perpetuating mechanisms seems to be at least as important as failure of suppressing mechanisms. Second, the two time-points, t1 and t2, are highly relevant clinically (Fig. 2.1): time-point t1 indicates when a seizure is abnormally prolonged and unlikely to stop spontaneously in a given time. There is good evidence from clinical research that this is at 5 min for generalized tonic–clonic seizures [11–14]. There is some evidence that t1 is at about 10 min in focal seizures with or without impairment of consciousness [14]. Thus, in general, t1 is the time when treatment should be started. In individual patients there may be some variability based on prior history and comorbidities. Time-point t2 marks the time at which neuronal damage or alteration of neuronal networks may begin, highlighting the need for aggressive treatment to prevent SE from reaching this stage. Again, as knowledge is incomplete, but given the experimental evidence indicating irreversible brain damage after

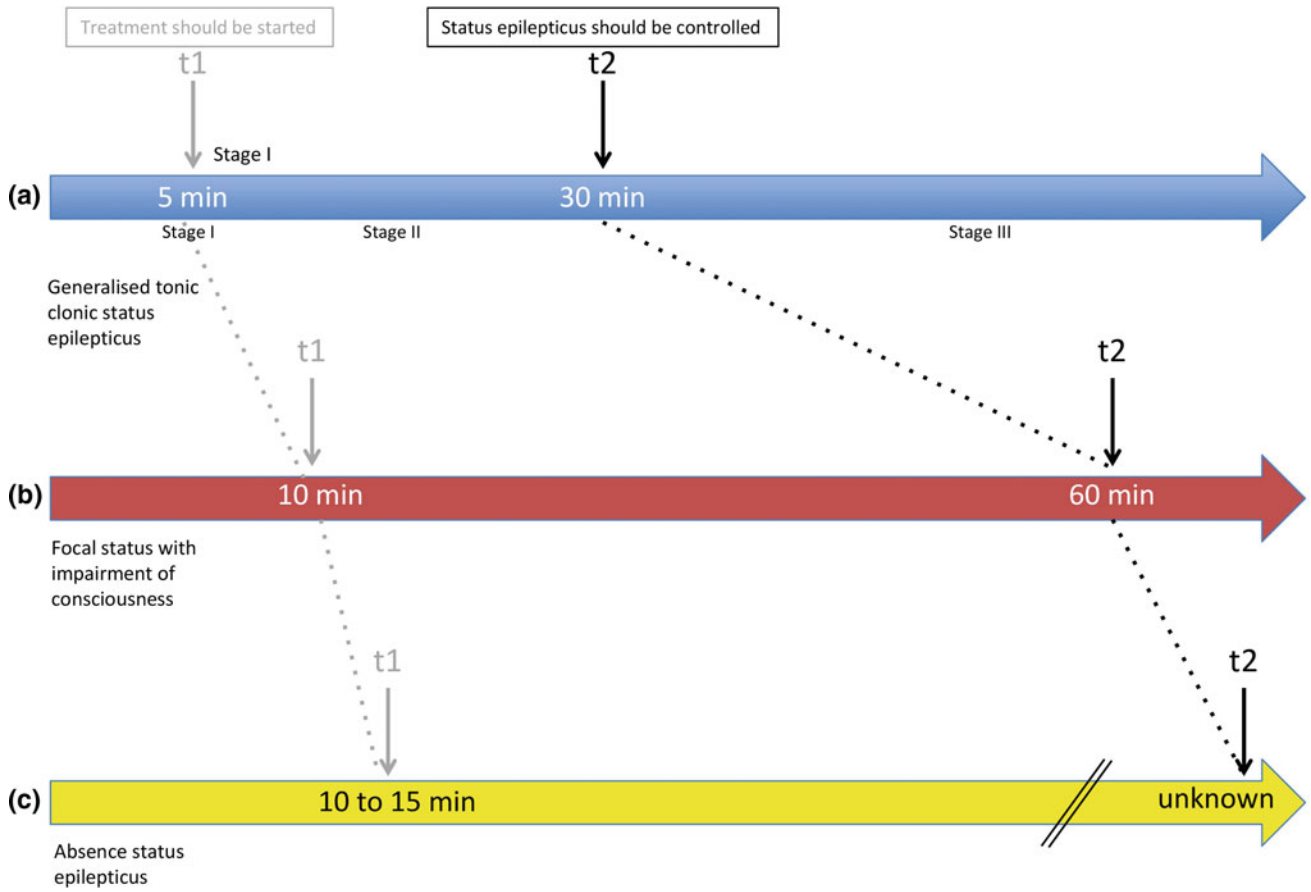

Fig. 2.1 Operational dimensions with *t1* indicating the time that emergency treatment of status epilepticus should be started and *t2* denoting the time at which long-term consequences may be expected. Time (*t1*), when a seizure is likely to be prolonged leading to continuous seizure activity. Time (*t2*), when a seizure may cause long-term consequences (including neuronal injury, neuronal death, alteration of neuronal networks and functional deficits). For generalized tonic-clonic status the stages have been added (*stage I* 5–10 min; *stage II* 10–30 min; *stage III* 30–30 min)

prolonged seizures [15] and the potential threat of brain damage in humans, the Task Force proposed the continued use of 30 min as time-point t2 in convulsive SE. There is only limited (or no) evidence for when neuronal damage takes place in other forms of SE [8, 15]. Imaging studies in humans suggest that cytotoxic edema occurs after prolonged seizure activity, so t2 was set at 60 min for focal status with impairment of consciousness. The timelines were set primarily for operational purposes, and the timing of the onset of brain damage may vary considerably with age, intensity of SE, and other clinical circumstances. It was the intention of the Task Force to choose time t2 to help provide a practical safe guideline for clinical purposes [8].

The framework for the new 2015 classification was built on four axes: (1) semiology, (2) etiology, (3) EEG correlates, and (4) age. The backbone of the classification is the semiology. Here, the different clinically identifiable forms of SE were divided along two taxonomic aspects: motor activity and impairment of consciousness, yielding two major groups: (A) SE with prominent motor symptoms, including all convulsive forms, and (B) SE without prominent motor symptoms representing the nonconvulsive forms of SE (NCSE) (Table 2.3). Each group can be divided again according to the degree of impairment of consciousness, which is highly relevant clinically. NCSE with coma represents a life-threatening condition that requires urgent and intensive treatment, whereas NCSE without coma occurs most often in the form of absence SE or focal SE with impairment of consciousness (previously called "complex partial SE"), which are often far easier to control than the forms of NCSE associated with coma [16].

The etiology of status is divided into two groups: (1) known or symptomatic, and (2) unknown or cryptogenic. The symptomatic group can be subdivided into acute symptomatic, remote symptomatic, and progressive symptomatic. A list of known causes of SE is added in an

Table 2.3 Axis 1 (Semiology): International League Against Epilepsy (ILAE) classification of status epilepticus (From Trinka et al. [8], with permission)

A. With prominent motor symptoms
1. Convulsive status epilepticus (CSE; synonym: tonic-clonic SE)
a. Generalized convulsive
b. Focal onset evolving into bilateral convulsive SE
c. Unknown whether focal or generalized
2. Myoclonic status epilepticus (prominent epileptic myoclonic jerks)
a. With coma
b. Without coma
3. Focal motor status epilepticus
a. Repeated focal motor seizures (Jacksonian)
b. *Epilepsia partialis continua*
c. Adversive status
d. Oculoclonic status
e. Ictal paresis (i.e. focal inhibitory SE)
4. Tonic status epilepticus
5. Hyperkinetic SE
B. Without prominent motor symptoms (i.e. nonconvulsive status epilepticus, NCSE)
1. NCSE with coma (including so-called "subtle" SE)
2. NCSE without coma
a. Generalized
i. Typical absence status
ii. Atypical absence status
iii. Myoclonic absence status
b. Focal
i. Without impairment of consciousness (aura continua, with autonomic, sensory, visual, olfactory, gustatory, emotional/psychic/experiential, or auditory symptoms)
ii. Aphasic status
iii. With impaired consciousness
c. Unknown whether focal or generalized
Autonomic SE

appendix to the classification and can be used as a syllabus; this needs to be updated periodically as new information emerges. SE often occurs in the context of genetic epilepsy syndromes, but there is essentially always a trigger for the status itself, such as fever, electrolyte disturbance, or other intrinsic factors.

The third axis includes the electroencephalography (EEG) correlates of the SE. In convulsive SE, the clinical presentation is most often clear, and artifacts obscure the EEG, rendering the EEG of little value. The opposite is true for the nonconvulsive forms of SE (category B in axis 1), where a correct diagnosis is often not possible without EEG. In the most extreme forms, the patient is in deep coma and only an EEG can show the epileptiform or rhythmic discharges leading to the diagnosis [16, 17]. Nevertheless, caution is appropriate here. There is currently no clear consensus as to which EEG patterns in coma represent SE. Therefore, the group recommended describing the EEG correlate of status in a given patient using the following descriptors: name of pattern, morphology, location, time-related features, modulation, and effect of intervention, and to use the recently proposed terminology from the American Clinical Neurophysiology Society [18] and its diagnostic EEG criteria for NCSE [17, 19–21] as a practical guide for diagnosis. With the new definition, there is hope to give clinicians better guidance as to when to treat, how aggressively to treat, and how to avoid over- or under-treatment of SE [22].

There are, of course, other clear directions for future research, e.g., concerning the time of t1 in the absence status, myoclonic status, and other forms of SE, which are completely unknown. Also, it must be emphasized that the idea of t1 was derived from a population with drug-resistant epilepsy undergoing video-EEG monitoring. Acute

symptomatic seizures may behave differently. The same is true for t2, and the time-points given here are for operational purposes, remaining fully aware that current knowledge is very limited. This classification of SE is the first attempt to not mirror the seizure classification system *per se* [8]. It is hoped that the use of two clinically accessible taxonomic criteria, namely motor activity and disturbance of consciousness, will lead to a broad acceptance by clinicians dealing with SE. Much research is necessary to determine whether the diagnosis of SE also includes boundary syndromes such as epileptic encephalopathies, coma with non-evolving epileptiform EEG patterns, behavioral disturbances (e.g., psychosis) in patients with epilepsy, or acute confusional states (e.g., delirium) with epileptiform EEG patterns [17, 23].

The new classification has already undergone a feasibility study by two members of the Task Force. They retrospectively assessed 488 episodes of SE and classified them according to previous clinical terminology and by the new classification system. Generalized convulsive SE occurred in 230 patients (47%), and nonconvulsive SE in coma in 29 (6%); these two categories corresponded almost perfectly between the two classifications. Focal SE, however, was markedly heterogeneous, and the new classification appeared to better reflect the clinical reality, offering more relevant subdivisions, which also differed in mortality rates [24].

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The Epidemiology of Status Epilepticus

3

Elizabeth J. Waterhouse

Introduction

Although prolonged seizure states have been recognized since ancient times, the frequent occurrence of status epilepticus (SE) was not fully appreciated until the 1990s. Even in the twenty-first century, SE continues to challenge clinicians and investigators. Despite recent advances in its diagnosis and treatment, and the widespread availability of sophisticated intensive care units, SE is associated with a persistently high fatality rate. In 1997, inpatient medical costs relating to SE were estimated at $3.8–$7 billion dollars annually in the United States alone, which when adjusted for inflation equates to $5.6–$10.4 billion today [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 its initial manifestation. In addition, it frequently occurs de novo in the setting of other systemic and neurologic conditions that 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.

Key epidemiologic studies in the United States and Europe have documented the incidence, etiologies, and mortality of SE, using geographically defined populations. More recently, to characterize SE further, researchers have turned to "big data," analyzing national data sets of coded information on hundreds of thousands of individuals. This chapter reviews the literature regarding the epidemiology of SE from early studies until the present.

E.J. Waterhouse (✉)
Department of Neurology, Virginia Commonwealth University School of Medicine, 1101 East Marshall Street, Box 980599Richmond, VA 23298-0599, USA
e-mail: elizabeth.waterhouse@vcuhealth.org

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Early Studies of Status Epilepticus

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 at least one 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-year period [7], to 0.13% of all casualty visits to a Helsinki university hospital over 1 year [8], to 3.5% of all admissions to two neurologic intensive care units over an 8-year 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 180–280 persons with convulsive SE per one million population per year [16]. Shorvon augmented this tally by adding estimates of absence SE, complex partial SE, neonatal SE, nonconvulsive SE (NCSE), and other SE syndromes, and calculated the estimated total annual incidence of all SE to be about 500 (441–646) cases per million in the general population [3].

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 nineteenth and early twentieth century came from specialized hospital settings, which likely skewed the results toward higher mortality rates. Case fatality 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 death rates ranging from 3 to 11% in children, and 14 to 59% in adults. Totaling the cases in the various studies, case fatality following SE was 7% for children, 28% for adults, and 18% overall [3]. The majority of deaths were attributed to the underlying cause of the SE.

Definition

The heterogeneity of cases labeled as SE in the early studies emphasized the need to establish a standard definition of SE. In 1993, the Working Group on SE convened by the Epilepsy Foundation of America defined SE as "more than 30 min of continuous seizure activity, or two or more sequential seizures without full recovery of consciousness between seizures" [19], This definition was used by the key population-based epidemiologic studies listed in Table 3.1 [20–28].

Over the past two decades, both clinicians and researchers have argued for an operational definition that is shorter than 30 min. These arguments in part rely upon several studies that found that a generalized convulsive seizure lasts, on average, about 60 s and rarely exceeds 2 min [29–31]. Thus seizures lasting longer than several minutes are unlikely to cease spontaneously and may be more appropriately grouped with SE episodes of longer duration. Acknowledging the clinical goal of early and successful treatment once impending SE is recognized, SE durations of 20, 10, and finally 5 min were advocated [32–34].

In 2015 the International League Against Epilepsy task force proposed a conceptual definition that incorporates two time points: t_1 indicates when treatment should be initiated, and t_2 marks the point after which long-term consequences may appear [35]. The proposed definition states: "Status epilepticus is a condition resulting either from the failure of the mechanisms responsible for seizure termination or from the initiation of mechanisms which lead to abnormally prolonged seizures (after time point t_1). It is a condition which can have long-term consequences (after time t_2), including neuronal death, neuronal injury, and alteration of neuronal networks depending on the type and duration of seizures." In the case of convulsive SE, t_1 and t_2 are estimated to be 5 and 30 min, respectively, based on clinical studies and animal experiments, but for other forms of SE, these time points are not known.

In reviewing clinical studies, it is important to recognize that the definition of SE used in clinical studies impacts the results and may even introduce bias. If a longer duration is used and 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 that used the 30-min definition of SE thus included patients who may have been predisposed toward more severe SE and worse outcomes. More recent studies using a shorter definition may be expected to show a higher incidence of SE and a lower mortality.

Methodologies

Population-Based Studies

Early studies consisted primarily of case series, which were important in documenting the types of SE, their relative frequencies, and common etiologies. In order to determine the incidence of a condition such as SE, one must define a population, and then attempt to capture and document every case, over a defined time interval, usually at least a year, and often much longer. Such studies generally focus on a city, county, or defined community and then seek to capture every case that occurs. The active ascertainment process involves identifying cases using multiple strategic data sources such as ambulance reports, emergency department visits, hospital admissions, medical records, consultation requests, electroenchepalography (EEG) reports, telephone referrals, and so forth. Cases are then reviewed, confirming or excluding cases based on the study's criteria for SE. By tabulating all cases, and using total population data from the defined region, incidence rate, mortality, and other population-based parameters can be calculated. Although time- and labor-intensive, such studies provide valuable information with a degree of accuracy that reflects the diligence of the surveillance.

Large National Data Sets

Over the past decade, studies of large data sets have yielded a different type of information. In addition to demographic information, data sets from the Centers for Disease Control and Prevention, the Nationwide Inpatient Sample, and the National Hospital Discharge Survey contain coded diagnostic information, such as hospital discharges, complications and comorbidities, and death certificate diagnoses.

Table 3.1 A summary of the results of seven population-based Epidemiology studies of status epilepticus

Location of study, Reference, (year published)	*N*	Annual incidence (per 100,000)	Epilepsy prior to SE	Most common etiology	Mortality/case fatality rate (%)	Other
Richmond, Virginia DeLorenzo et al. [20] (1995) DeLorenzo et al. [21] (1996)	166	41	42%	Infection/fever (children), Low ASD (adults)	22	Adults and children
Rochester, Minnesota Logroscino et al. [22] (1997) Hesdorffer et al. [23] (1998)	184 199	– 18.3[a]	– –	– Acute symptomatic 50%	19[b] –	Adults and children, retrospective
French-speaking Switzerland Coeytaux A et al. [24] (2000)	172	10.3[a]	43%	Acute symptomatic 63%	7.6[c]	Adults and children
Hessen, Germany Knake et al. [25] (2001)	150	17.1[a]	50%	Remote stroke 36%	9.3[c]	Adults only, mean age 65
Bologna, Italy Vignatelli et al. [26] (2003)	44	10.7[a]	39%	Acute symptomatic 34%, stroke 41%	39[c]	Adults and children
Rural Italy Vignatelli et al. [27] (2005)	27	11.6[a]	41%	Acute symptomatic 30%	7[c]	Adults only, mean age 75
La Reunion, France Bhalla et al. [28] 2014	65	10.8[a]	Excluded those with prior epilepsy	Stroke (28%)	18.5	Adults and children

The methods used to calculate the incidence and mortality rates varied among studies. See referenced articles for methodological details. [a]Age and/or sex-adjusted annual incidence; [b]Febrile SE excluded from this study of SE mortality; [c]Case fatality rate; *ASD* anti-seizure drugs

One drawback is that the data included in these resources are subject to coding errors, changes in coding patterns, and limitations in the codes themselves. For example, the International Code of Diseases, Ninth Revision (ICD-9) contains three codes for SE: 345.3—"grand mal status," 345.7—"epilepsia partialis continua," and 345.2—"petit mal" SE. A case of intermittent complex partial seizures without recovery of awareness in between might not even be recognized as SE or assigned an appropriate code.

The definition of SE has important implications for accuracy of coding. A validation study of the 345.3 ICD-9 code for SE ascertained cases of SE (including convulsive and nonconvulsive cases) that received a discharge code of 345.3 over 1 year at a large urban hospital. Also identified were cases with discharge records suggesting SE that were not overtly documented or coded as SE. Many more SE diagnoses were missed when a longer time-dependent SE definition was used. Using seizure duration as the criterion for SE, diagnostic sensitivity was 100% for 5 min. For SE lasting at least 10 min, however, sensitivity fell to 55%, and for SE lasting at least 20 min, it was just 14% [36].

Another study found that ICD-9 and ICD-10 coding accurately identified epilepsy, although validity of coding for specific types of epilepsy was suboptimal. Positive predictive value (PPV) for grand mal SE was 84% for ICD-9 coding and 100% for ICD-10, while the PPV for complex partial SE was 83% (ICD-10) [37]. Epilepsy was commonly miscoded with a nonspecific code for "convulsions." The authors concluded that accurate surveillance would require including the code for convulsions, with adjustment for the small number of cases labeled with this code who do not actually have epilepsy. These limitations in documenting and coding SE must be kept in mind when interpreting studies that rely on coding rather than careful case ascertainment through close examination of actual medical records.

What large data sets lack in terms of diagnostic accuracy and case ascertainment they make up for in size and breadth,

encompassing an enormous number of cases from all over the United States. Data have been collected over decades, allowing a broad view of trends over time. In these formats, SE data can be correlated, relatively easily, with other measures, including length of stay, concurrent medical conditions, procedures, and other parameters.

Population-Based Epidemiological Studies

The results of population-based epidemiologic studies are summarized in Table 3.1.

United States

Richmond, Virginia. The Richmond metropolitan area SE study collected data from both community hospitals and a tertiary referral university medical center. In this study, the SE team was notified as soon as SE was diagnosed, and data collection began. All types of SE lasting at least 30 min (continuous, or intermittent without regaining of consciousness) were included. 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 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 (all types) 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 [20]. These figures did not include repeat episodes of SE in a single patient. With validation of the database, it was determined that approximately 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 United States 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.

Rochester, Minnesota. A retrospective study from the Mayo Clinic, looked at SE in Rochester, Minnesota, between 1965 and 1984 [23]. 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-year period. The incidence of SE was 18.3 per 100,000. This is considerably lower than the incidence from the Richmond study, which may be due to different study methods (retrospective vs. prospective) and 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 below on Race and Status Epilepticus). The incidence rates of SE in the Richmond and Rochester studies are comparable when racial factors are taken into account.

Europe

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-day case fatality was 39% [26].

A 2-year population-based study of SE in adults in a rural region of Northern Italy reported an adjusted annual SE incidence of 11.6/100,000. The crude incidence in adults over age 60 was 38.6/100,000—more than 10-fold the value for younger individuals. Acute symptomatic SE, primarily due to cerebrovascular disease, accounted for 30% of cases. Although the risk factors for SE in rural and urban Italy were similar, the rural 30-day case fatality of 7% was much lower than the Bologna rate of 39%. The authors inferred that short-term prognosis was influenced by differences in health service organization [27].

Hessen, Germany. A prospective population-based study in Germany identified 150 adult patients with SE over a 2-year period [25]. 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%.

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-year period [24]. 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 one, and in the elderly, and higher among men than women. The case fatality rate was 7.6%.

Other Countries

La Reunion. La Reunion is a French overseas island territory east of Madagascar in the Indian Ocean. A population-based study, excluding patients with known epilepsy, found an incidence of 8.52 per 100,000 [28]. In this population, SE was most common in the elderly, and in men, and 60% of the SE was convulsive. Almost half of SE cases were provoked, by factors such as stroke, alcoholism, and infections. Mortality was 18.5%.

Large Data Sets

Table 3.2 [38–42] summarizes several studies of large data sets that rely on hospital coding.

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 [38]. 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 may 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%.

United States. An analysis of over 760,000 discharges with an ICD-0 diagnosis code of 345.3 ("grand mal status epilepticus") found an increasing incidence of SE in the United States over time, while mortality rates remained relatively stable. Between 1979 and 2010, SE incidence rose from 3.5 to 12.5 per 100,000, with the largest increases in the first and last decade. In-hospital mortality was 9.2%. Factors that may have influenced the rising incidence of SE include increased recognition of post-anoxic myoclonic SE, increased EEG availability, the evolving definition of SE with a shorter duration, and an expanding elderly population, among whom SE is more likely to occur [39].

Taiwan. A 12-year cohort study in Taiwan identified patients using a database of discharge diagnoses [41]. This study found an incidence of 4.61 per 100,000 person-years, and like other studies, confirmed a J-shaped age distribution. In-hospital mortality was lower in males (7.4%) than in females (11%). The authors postulated that the lower incidence they found may have been due to ethnic factors or due to methodological differences.

Thailand. In Thailand, statistics from a database of reimbursement claims found 5.1 SE cases per 100,000 adults over 1 year, with 12% mortality [43]. A longitudinal study found that SE incidence in adults rose steadily from 1.29 to 5.2 per 100,000 between 2004 and 2012. The in-hospital mortality was 8.4% [42]. Risk factors for poor outcome included female sex, age greater than 60, and primary care hospital location.

Developing Countries

There are few large-scale studies of SE in developing countries. Most of the information about SE in African

Table 3.2 A summary of the results of five studies that analyzed data from large national data sets

Location, Reference (Year published)	*N*	Annual incidence (per 100,000)	Case fatality rate/mortality	Other
California Wu et al. [38] (2002)	15,601	6.2	10.7%	Convulsive SE only
United States Dham et al. [39] (2014)	760,117[a]	12.5[b]	9.2%	All types of SE
United States Betjemann et al. [40] (2015)	408,304	13.86[b]	0.2 per 100,000[c]	All types of SE
Taiwan Ong et al. [41] (2015)	12,627	4.61	8.3%[d]	Convulsive SE only
Thailand Timkao et al. [42] (2015)	12,367	5.2	8.4%[e]	All types of SE, adults only

The methods used to calculate incidence and death rates varied among studies. See text and referenced articles for methodological details. [a]SE discharges over a 32-year interval; [b]in 2010; [c]age-standardized, [d]in-hospital case fatality rate, [e]in 2012

countries comes from case series and cohort studies that suggest that SE is at least as common as in more developed countries. An 11-year study of SE in Senegal documented 697 cases, with a mortality rate of 24.8% [44]. The most common etiology was infection (67%), followed by epilepsy. In Nigeria, 41 cases were diagnosed over a 10-year period at University College Hospital in Ibadan, with the most common etiology being CNS infection (41%) [45]. The incidence of SE in a cohort study of Kenyan children was 35/100,000 [46].

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 [47]. One study looked at infantile SE, and found 139 infants treated for SE at two Tunisian hospitals over a 7-year period. The mortality was 15.8% and the most frequent causes were fever and acute symptomatic diagnoses [48]. Several other studies of epilepsy suggest that SE is a common cause of death in epilepsy patients in Africa [49–51].

Mortality

In most of the population-based studies discussed here, mortality is defined as death within 30 days 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% [21]. In the Rochester, Minn. population, 30-day mortality was 19% following a first episode of SE. Short-term mortality was associated with an underlying acute symptomatic etiology [22]. Mortalities and case fatality rates in other epidemiologic studies ranged from 7.6 to 39% (see Table 3.1). Clinical factors influencing mortality are discussed further in the section below, Determinants of Mortality in Status Epilepticus.

Large data set studies have found lower case fatality rates and lower SE incidence than older population-based studies (see Table 3.2). In-hospital mortality was 9.2% for generalized convulsive SE in the National Hospital Discharge Survey [39]. The calculated mortality rate based on the underlying cause of death from death certificate data was 2 per million in 2010 [40]. The discrepancy between this low mortality rate and the much higher rates of previous studies is due to different approaches in assessing mortality. This study counted deaths for which SE was listed on the death certificate as an underlying cause, while other studies included in their rates all subjects with SE who died, regardless of the cause.

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% [52]. This mortality is not associated with SE duration and may be due to serious comorbid conditions, most commonly recent or remote stroke.

Time Trends in Incidence and Mortality

Longitudinal data demonstrate an increase in SE incidence, while case fatality rates have remained stable. In the Rochester, Minn. 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, approximately 16% of SE was myoclonic SE, usually in the setting of anoxic encephalopathy following cardiac arrest in the elderly [53]. SE etiologies remained similar over the two decades spanning 1970–1989 [54].

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 1935–1944 and 1945–1954 and increased modestly thereafter to 2.7 per 100,000 for 1975–1984 [53].

Despite rising incidence rates, mortality rates increased only slightly between 1955 and 1984, from 3.6 to 4.0 per 100,000, and the 30-day case fatality rate was unchanged [53]. When cases of myoclonic SE were excluded from analysis, SE survival improved during 1975–1984, compared with previous decades [23, 53].

Large data set studies also report a growing incidence of SE without a corresponding bump in mortality. A study of 32 years of U.S. National Hospital Discharge Survey data found that SE incidence increased nearly fourfold, while mortality remained relatively unchanged [39]. Another study of SE-related hospitalization over 12 years found that SE incidence increased 56% between 1999 and 2010, while SE-related mortality rose just 5.6% [40]. The largest increase in SE incidence occurred in intubated patients for whom SE was not the principal diagnosis, suggesting better recognition of SE in ICU patients, possibly due to EEG monitoring.

Age and Status Epilepticus

There is a bimodal distribution of incidence of SE, with the highest values during the first year of life and after age 60 years. In adults, the elderly have the highest risk for

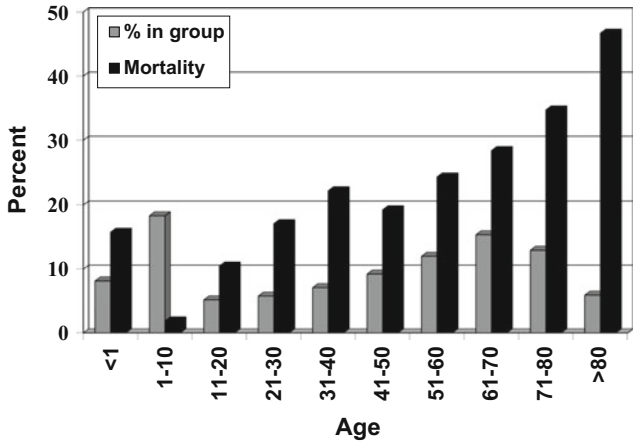

Fig. 3.1 Distribution by age of 2025 patients in the Richmond Metropolitan Area Status Epilepticus Database. The *dark bars* denote the percentage of patients who died within each age group

developing SE, with an incidence of 86 per 100,000 per year [20]. Among children 16 years of age or younger, infants under the age of 1 year have the highest incidence, 156 per 100,000 per year [20]. Other studies have confirmed that the age distribution of SE is U-shaped, with peaks under 1 year of age and over 60 [23, 24, 38, 39]. 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 [21, 35].

Risk of SE-associated death increases sharply with age. Figure 3.1 illustrates mortality by decade, in 2025 cases from the Richmond SE database [55].

Sex and Status Epilepticus

There are conflicting reports regarding differences in SE incidence between males and females. In some studies, there were no significant differences [26, 38], but others found a greater incidence in males [23–25, 39]. 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 [23]. 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 [25].

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 days as women. Even when the analysis was restricted to SE associated with cerebrovascular disease and anoxic encephalopathy in the elderly, the increased risk persisted [22]. In a large database of hospital discharges, the in-hospital case fatality rate was 9.3% for males and 9% for females [39].

Race and Status Epilepticus

SE incidence rates are higher in African–Americans than in Caucasians in all age groups. In Virginia, the incidence of SE in Caucasians was 23 per 100,000 and 57 per 100,000 for African–Americans [21]. 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) [38]. Nevertheless, race is not an independent predictor of mortality [56]. The fatality rate following SE is much lower in African–Americans (17%) than in Caucasians (31%) [21]. The National Hospital Discharge Survey study confirmed a higher incidence of SE and lower case fatality rate in African–Americans [39]. Among children in North London, United Kingdom, ethnic and socioeconomic factors independently affected risk for prolonged febrile seizures and acute symptomatic convulsive SE [57].

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 3.1, 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 years) [21]. Patients who had low anti-seizure drug (ASD) 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%) [56]. A very low rate of prior epilepsy (3.8%) reported in a national database study of SE may reflect under-coding [39].

Risk of Epilepsy After Status Epilepticus

A prospective study identified patients without a previous history of epilepsy, who had de novo SE. After a median follow-up of 10 months, 58% of survivors developed epilepsy. An SE duration exceeding 24 h independently predicted the development of epilepsy [58].

Status Epilepticus 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 ASD levels (34%), followed by remote symptomatic events (including old stroke, hemorrhage, tumor, or trauma) (25%) and stroke (22%) [21].

Status Epilepticus and Cerebrovascular Disease

SE occurs in 1.1–1.4% of first-time stroke patients [59, 60]. In most studies, stroke is a major etiology for SE in older adults. When ischemic stroke and cerebral hemorrhages, both acute and remote, are considered together, cerebrovascular disease is associated with 41% of adult SE cases [20]. Stroke was also the most common etiology of SE in European studies [25, 26]. In the California study of 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%) [38]. A study at a large urban hospital in the 1980s found that ASD withdrawal, rather than stroke, was the most common cause of SE in adults, with alcohol-related causes the second most common etiology [54].

SE Etiologies and Mortality

The etiology associated with the highest mortality in the Richmond study was anoxia [21, 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 days [22]. Low ASD levels had a mortality of only 4% [43]. Other studies reporting low overall SE mortality included a high percentage of patients with ASD withdrawal and alcohol-related etiologies [54]. Low mortality has been associated with unknown or remote symptomatic etiology [38, 61].

Status Epilepticus 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 ASD levels in 21% of children with SE [20].

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) [21, 27]. 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 [21]. 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% [21].

Absence SE was uncommon in the Richmond and Bologna populations [26]. In the Rochester study, it was also uncommon, but of the six cases, two occurred in adults [23]. 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%) [24, 25].

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% [21]. Mortality rates for secondarily generalized SE ranged from 22 to 47% [22, 26]. Absence SE was not associated with any significant mortality, while mortality following myoclonic SE was as high as 68% [22, 26]. Seizure type was not a significant independent risk factor for mortality [22, 56].

Duration of Status Epilepticus

Older 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 this definition of SE. Although an operational SE definition of 5 min is now widely accepted, 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 [62]. The case fatality rate for those with seizures lasting 10–29 min was just 3%, compared to 19% for SE lasting at least 30 min. 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. Based on this information, studies defining SE with a shorter duration would be

expected to show an increase in SE incidence, without a corresponding rise in mortality. Recent studies using large national data sets have borne this out [39, 40].

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 [63]. 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.

Most studies have demonstrated that longer duration of SE is associated with worse outcome [7, 54, 61]. Lowenstein and Alldredge found that there was a significant relationship between duration of SE and response to treatment [7]. While 80% of patients who received treatment within 30 min of SE onset responded to first-line drugs, the response rate declined progressively with delayed treatment. Over 60% of patients in whom therapy was initiated after 2 h 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 [22]. This study was retrospective, and it is possible that ictal times were not always clearly documented or accurate.

In the Richmond population, the mean SE duration was 2 h, and the distribution was skewed toward longer times [56]. 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.

Determinants of Mortality in Status Epilepticus

Initial clinical studies of SE demonstrated the important contributions of etiology and seizure duration in determining mortality [14, 22, 23, 33, 54, 56, 64–66]. 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 [56].

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 approximately 39% in the odds ratio. SE had a higher incidence and a dramatic increase in mortality in SE in the elderly.

Etiology is a major determinant of SE prognosis. In a multivariate analysis, anoxia was the only etiology significantly associated with mortality, independently of other variables [20]. Although alcohol-related SE and SE related to low ASD 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 [54].

The relationship between SE etiology and mortality remains controversial. For critically ill SE patients with conditions such as cerebral anoxia, most believe that the underlying disease process, rather than SE itself, drives outcome [67]. Still, 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 synergistic effect of SE and stroke on mortality [68]. Further studies are needed to examine the relative contributions of SE itself, and its underlying etiologies, to the outcome of SE.

Recurrence of Status Epilepticus

Correlation with Age

Overall, SE recurs in about 13% of patients. Recurrent SE is more common in children than in other age groups, with recurrence rates of 17–35% in children, 7% in adults, and 10% in the elderly [20, 69]. Among children, SE was most common in those under the age of 1 year [20]. Of patients under the age of 4 years, 43% had a repeat episode of SE [21].

Risk Factors for Recurrent Status Epilepticus

In a population-based study of 183 first episodes of afebrile SE in Minnesota, SE recurred within 10 years in about one-third of subjects. Those with a progressive brain disorder all had SE recurrence, while 25% of those with other

etiologies had recurrence. Risk factors for recurrence were female gender and lack of response to the first medication. Those with partial SE and those whose SE responded to the initial treatment had a lower risk of recurrent SE [70].

A study of 95 children found that SE recurred more frequently in neurologically abnormal children, and in those with idiopathic or progressive neurologic SE etiologies [69]. Among all age groups SE recurred significantly more often in children, females, those with remote or withdrawal etiology, prior seizures, and partial seizures in the setting of coma [71].

Refractory Status Epilepticus

SE is usually described as refractory if it persists despite adequate doses of a benzodiazepine and an adequate loading dose of an intravenous ASD. The incidence of refractory SE has been projected to be between 2000 and 6000 cases per year in the United States [72]. Refractoriness to first- and second-line treatment occurs in 9–31% of SE patients [33, 73, 74].

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 93% 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% [33, 75].

A retrospective analysis of data from a Finnish intensive care consortium identified 395 adults with ICU-treated refractory SE, of whom 87 had super-refractory SE (SRSE). SRSE was defined as SE that continued or recurred 24 h or more after onset of anesthetic therapy. Post-anoxic etiologies were excluded. The calculated annual incidence of SRSE was 0.7 per 100,000, and the 1-year case fatality rates were 36% for SRSE and 22% for SE [76].

Refractory Status Epilepticus in Children

Mortality rates for adults with refractory SE are high, ranging from 39 to 48% [73, 77]. In children, refractory SE is frequently fatal, with case fatality rates of 16–43.5% [78–80]. Higher mortality is related to young age and etiology, with worse prognosis associated with acute symptomatic etiology and progressive encephalopathy [78]. Children with a multifocal or generalized abnormality on EEG at onset of SE had a higher mortality than those with focal abnormalities [78]. 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 [81]. Morbidity was substantial—all had intractable epilepsy, and none returned to neurologic baseline.

Risk Factors for Refractory Status Epilepticus

Few studies have assessed risk factors for refractory SE. Acute CNS etiologies and male sex were independent risk factors for refractory SE in one study, while patients with a history of prior seizures had a significantly lower risk [63]. In a retrospective study of 83 episodes of SE at a large academic teaching hospital, 69% continued to seize following a benzodiazepine, and 31% were refractory to treatment with a second anticonvulsant [74]. Independent risk factors for refractory SE in this study were NCSE 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 [74].

Status Epilepticus in Special Populations

Status Epilepticus in Children

Status Epilepticus Incidence in Children. Among children between 1 month and 16 years of age, SE is most common in the very young, with more than 40% of cases occurring in those under the age of 2 years [82]. The cumulative incidence of SE was about 1 per 1000 by 1 year of age [23]. In Richmond, Virginia, the annual incidence of SE in children under 16 was 38 per 100,000 [20]. In Switzerland, the incidence was similar for younger children (38.7 per 100,000 in children aged 0–4 years) but lower for older children (10.9 per 100,000 in ages 5–14 years) [24]. The incidence of a first-ever episode of convulsive SE in North London, U.K., was 18–20 per 100,000 children per year [83].

Etiologies of Pediatric Status Epilepticus. The most common etiologies for pediatric SE are non-CNS infection/fever (52%), remote causes (39%), and decreased ASD levels (21%) [21]. Etiologies vary according to age, however, with more than 80% of children under the age of two having febrile or acute symptomatic etiology, while older children are more likely to have cryptogenic or remote

symptomatic causes [82]. SE commonly occurs as the initial event in infants with unprovoked or acute symptomatic seizures, more so than for any other age group [23].

Risk Factors for Pediatric Status Epilepticus. In a series of 394 children with SE, 40% had previously documented neurologic abnormalities, and about half had a history of earlier seizures [82]. Risks differed depending on whether the children were younger or older than age 2 years. In children under 2 years of age, SE occurred more often in those who were neurologically normal, without a history of unprovoked seizures, while in older children, SE occurred primarily in those with prior unprovoked seizures, who were often neurologically abnormal [82].

Epilepsy is an important risk factor for SE in children. Ten to 20% of patients with epilepsy will have an episode of SE [84]. 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 years or younger, and partial seizures [85].

Seizure Characteristics. Generalized convulsive seizures are the major seizure type for pediatric SE, constituting about two-thirds of SE in children [84]. 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 [23, 86]. Children under the age of 1 year are more likely to have SE lasting over 2 h than briefer episodes [23].

Mortality. In general, the morbidity and mortality associated with SE in children are low and are primarily a function of etiology [82, 87]. The overall case fatality rate of SE in pediatric patients is 0–10% [14, 15, 20, 86, 88, 89], dramatically lower than that in adults or the elderly. SE-associated death in children is usually related to infection [20]. The occurrence of SE does not alter the mortality rates of children with epilepsy [85].

Febrile Status Epilepticus. Febrile seizures occur in 2–5% of children in the United States and Western Europe [87]. Case series suggest that about 4–5% of childhood febrile seizures last at least 30 min and thus qualify as SE [87, 90–96]. Febrile SE comprises more than 50% of all SE in children. It is most common under the age of 4 years [20, 23, 87].

In a study of 180 children with febrile SE, 74% presented with SE as the initial febrile seizure [87]. 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 [90, 92, 93]. Risk factors for febrile SE included neurologic abnormality, history of neonatal seizures, and family history of epilepsy [87].

Status Epilepticus 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 [97–99]. 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 [100]. In three of the monozygotic twin pairs, there was a history of SE in both twins; none of the dizygotic twin pairs was 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.

Status Epilepticus in the Elderly

Status Epilepticus 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 [21, 38]. 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 18–59 [25]. When the elderly population is further subdivided into age groups of 60–69 years of age, 70–79 years, and >80 years, each of these subgroups demonstrates an incidence of over 80 cases of SE per year per 100,000 individuals, but the highest incidence is in the 70–79-year-old subgroup—100 per 100,000 individuals per year [101]. Almost 0.4% of people who survive to age 75 will have had an episode of SE [23].

Status Epilepticus 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, 101–103]. In the Richmond study, the most common etiologies of SE in the elderly were: stroke 21%, remote symptomatic 21%, low ASD 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% [101]. The Rochester, Minnesota study suggests that dementia is another common cause of SE in the elderly [23]. 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 [20].

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% [25]. 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 [38]. SE affects a significant proportion of stroke survivors. During a mean follow-up interval of almost 4 years, SE occurred in 9% of ischemic stroke patients [104, 105].

Status Epilepticus 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% [20, 21]. 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 ASD levels, alcohol withdrawal, and idiopathic etiologies each had a mortality of less than 6%. Remote symptomatic cases (mostly prior strokes) had a 14% mortality [101].

Seizure Types in the Elderly. The most common seizure type in elderly people with SE is partial with secondary generalization (45%). 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% [101].

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 [106]. 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 [107].

Status Epilepticus in the Intensive Care Unit

There are two categories of SE patients in the intensive care unit (ICU)—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 [108]. 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. In critically ill patients with coma or altered mental status, continuous EEG monitoring has detected NCSE in 8–30%, and nonconvulsive seizures in even higher proportions (see Chap. 23, "Continuous EEG Monitoring for Status Epilepticus"). The highest rates of NCSE were found in patients with encephalitis, traumatic brain injury, and hypoxic-ischemic encephalopathy, emphasizing the importance of EEG monitoring in ICU patients with altered mental status or coma [67, 108–110].

Even in patients in whom SE is easily diagnosed due to obvious generalized convulsive seizures, it is important to obtain an EEG. NCSE and seizures frequently continue after clinical seizure activity has stopped. One study found that 14% of patients who stopped seizing clinically continued to seize electrographically, and 34% had recurrent seizures, of which over two-thirds were nonconvulsive [111]. In a study of patients with generalized electrographic SE, 40% had been diagnosed with clinical SE and were thought to have stopped seizing [112].

Conclusions

Epidemiologic data suggest that SE is a relatively 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 risk of death following SE in children is very low, death rates climb significantly for the elderly. The independent determinants of mortality following SE are age, seizure duration, and etiology.

Both population-based studies and recent analyses of large national data sets provide valuable insights, but their results must be considered in light of the definitions and methodologies used. The rising incidence and relatively stable mortality of SE over time likely reflect the adoption of a shorter duration definition of SE, as well as improved SE recognition with continuous EEG monitoring. Information gained from this research allows us to more accurately assess the risks of developing SE and surviving SE in diverse populations.

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Nonepileptic Psychogenic Status Epilepticus

4

Benjamin Tolchin and Barbara A. Dworetzky

Introduction

Psychogenic nonepileptic seizures (PNES) are paroxysmal events involving involuntary movements, alterations in consciousness, or both, without associated electroencephalography (EEG) changes, caused by psychological factors. PNES may appear similar to, or even clinically indistinguishable from, most forms of epileptic seizures. PNES constitute the largest group of functional neurologic symptom disorders, and are thought to be outside of patients' conscious control in the large majority of cases [1, 2]. They are believed to be caused by high levels of stress and other psychologically disturbing affective problems in patients who have difficulty in recognizing, understanding, and processing their emotions. There are also rare documented cases of patients consciously producing PNES in order to inhabit the "sick role" or obtain some secondary gain (disability, a legal settlement, etc.)—in which rare cases the PNES are a form of factitious disorder or malingering [3, 4]. PNES occur and are described similarly across many ethnicities and cultures, in both developed and developing countries [5–7].

The disability and healthcare costs incurred by PNES are significant. Patients' and families' ratings of disability in PNES are as severe as those in epilepsy [8]. Patients with PNES are economically and socially dependent, have frequent emergency department visits and hospital admissions, and incur high medical care costs [9–11]. Up to 75% of patients continue to have their episodes and associated disability at 5–10 years' follow-up [9, 12, 13]. PNES have been associated with modest excess premature mortality, with some from increased suicidality and to a lesser extent from iatrogenic causes [14–16].

Nonepileptic psychogenic status epilepticus (NEPS) is defined as a prolonged episode of PNES. Other historical terms for the same condition have included "pseudostatus epilepticus" and "status pseudoepilepticus" [17]. The precise duration of PNES necessary to constitute NEPS has varied among epileptologists and among studies, but in one survey of epileptologists the majority considered the threshold duration to be >20 min [18]. NEPS is easily mistaken for status epilepticus (SE). Consequently, among patients with PNES, those with NEPS are more likely to present via the emergency department [19, 20], receive IV medications [21, 22], undergo intubation for airway protection [23], and suffer iatrogenic complications and mortality [18].

Epidemiology

Functional neurologic symptom disorders such as PNES are frequently encountered by neurologists—ultimately diagnosed in just over 5% of all new outpatient referrals [24]. PNES are diagnosed in 24–39% of patients admitted to epilepsy monitoring units [25–30]. The overall incidence of PNES is estimated to be up to 4 per 100,000 persons per year and the overall prevalence up to 33 per 100,000 persons, approximately 5% that of epilepsy [31]. The proportion of patients with PNES who also have epileptic seizures, once thought to be as high as 50%, is probably only about 10%, as demonstrated by more recent studies requiring video-EEG (vEEG) recording of typical episodes to make the diagnosis [27, 32, 33].

NEPS occurs in approximately 18–23% of patients with PNES, as documented by families of patients and by evaluations in epilepsy monitoring units (EMUs) [19, 34, 35]. In one study, 78% of PNES patients reported having had at least one prolonged episode ($\geq$ 30 min) in their lifetime, but this result differs significantly from the reports of families

B. Tolchin (✉) · B.A. Dworetzky
Department of Neurology, Brigham and Women's Hospital, Harvard Medical School, 75 Francis Street, Boston, MA 02115, USA
e-mail: btolchin@partners.org

B.A. Dworetzky
e-mail: bdworetzky@partners.org

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and of EMUs, and might reflect misperceptions by self-reporting patients [36]. Nevertheless, PNES tend to be of longer duration than epileptic seizures: the majority of epileptic seizures last <2 min, whereas the majority of PNES episodes are >2 min in duration [36–38].

Distinguishing Characteristics of NEPS Versus Intermittent PNES

One active area of research has been the identification of characteristics distinguishing patients with NEPS from those who have non-prolonged PNES, with events lasting <20 min. These patients are sometimes identified as having intermittent PNES, or iPNES. Thus far, four studies have sought and failed to identify consistently distinguishing features among the demographics, clinical characteristics, or personality characteristics of patients with NEPS in comparison to those with iPNES [19, 34–36]. To researchers' surprise, patients with NEPS were not found to have more frequent or more severe histories of abuse, head trauma, psychiatric comorbidities, tendencies toward somatization or dissociation, or other personality abnormalities. One study [36] found that patients with NEPS were on average younger than patients with iPNES, and trended toward higher scores on personality scales measuring proclivity for self-harm, but these findings were not replicated in the other studies. Another study [19] found that patients with NEPS were diagnosed more quickly after symptom onset, but this finding also was not replicated and remains controversial [34]. One study looking at semiologies [20] found that patients with NEPS have more varied semiologies than patients with iPNES (e.g., more likely to include convulsions), but this finding has also not been replicated and may be the result of NEPS involving more prolonged events that witnesses can describe in greater detail. The existing studies are limited in that they are all retrospective or small single center studies, and the possibility remains that a large multicenter prospective study might identify distinguishing features of NEPS in comparison to iPNES. Nevertheless, the tentative conclusion of the few existing studies to date is that NEPS is not a distinct entity, but rather a relatively common manifestation within the continuum of PNES [34, 35].

Beyond the four studies cited above, there is relatively little research specifically focused on NEPS, as opposed to PNES more generally. Patients with NEPS typically present to the emergency department, are often admitted to the ICU, and are frequently discharged as soon as it becomes apparent that they do not have SE. NEPS occurring during elective admissions to the EMU are less common [20]. As a result, it is difficult to recruit and follow these patients prospectively. For this reason, much of the available research on diagnosis, treatment, and prognosis is performed in the general population of patients with PNES. The findings are presumed to apply to the subpopulation of patients with NEPS because clinical and personality characteristics appear to be similar between patients with NEPS and iPNES. Still, many findings in this review have not been independently confirmed in the subpopulation of patients with NEPS.

Distinguishing Characteristics of NEPS Versus Status Epilepticus

For the clinician encountering a patient with possible NEPS, the most immediate concern is differentiating it from SE. The treating physician must first consider its possibility. Difficulties arise in the emergency department or intensive care unit (ICU) settings, where suspected SE may trigger a predetermined protocol for the management of SE, so it is optimal to make the diagnoses of PNES and NEPS before the patient presents to the ED. The clinical history, semiology, and (whenever possible) vEEG findings contribute to the diagnosis of NEPS versus SE. Clinicians should always consider the possibility of NEPS in emergency settings before the initiation of a potentially morbid iatrogenic drug protocol for purported status epilepticus, even when an EEG cannot be obtained. In such circumstances, clinicians may be faced with a Bayesian analysis of probabilities based on clinical history and semiology.

Demographics and Clinical History

In a patient presenting with possible SE, there are several clinical characteristics that may increase suspicion for a psychogenic as opposed to epileptic etiology. While consistent differences in age have not been found [38], patients with PNES are more often (approximately 75%) female [9, 39–41], and are more likely to have a history of sexual, physical, or emotional abuse (approximately 80% of cases, of which approximately half include sexual abuse) [42–44] and psychiatric comorbidities—found in approximately 70% of cases [45, 46]. Of note, one small study of *pediatric* patients with NEPS found similarly high rates of psychiatric comorbidities but found no history of abuse [22]. Rather, this study uniformly found acute stressors including changes in school, parental divorce, parental loss of employment, etc. This has been reported in the literature for pediatric PNES as well [47, 48] and suggests a different mechanism underlying NEPS and PNES in children.

Several studies have shown a higher event frequency among patients with PNES than among patients with epileptic seizures [36, 49, 50]. Indeed, given the greater

event frequency and duration seen with psychogenic seizures, patients with a prior diagnosis of epilepsy presenting with apparent recurrent status epilepticus should be carefully evaluated for NEPS [36]. One small single center study showed that a seizure frequency of at least 2 per week, refractory to at least 2 anti-seizure drugs and in combination with a history of 2 normal routine EEGs, has a positive predictive value of 85% for psychogenic seizures [50]. Another small study showed that a prior diagnosis of fibromyalgia or chronic pain syndrome in a patient presenting with seizures carries a positive predictive value of 75% for psychogenic seizures [51].

Importantly, none of the clinical characteristics discussed here rules out epileptic seizures or definitely confirms a diagnosis of PNES or NEPS. Indeed, patients with epilepsy are noted to have higher rates of abuse and psychiatric comorbidities than does the general population. Nonetheless, these factors may raise or lower the pretest probability of PNES and NEPS in the absence of definitive EEG data, and they are grounds for adjusting one's clinical suspicion.

While a history of psychological trauma, such as severe medical illness or physical, emotional, or sexual abuse may be helpful in raising suspicion for PNES or NEPS, the identification of a psychological stressor is not *necessary* to make the diagnosis. Prior editions of the Diagnostic and Statistical Manual of Mental Disorders (DSM) required the identification of a psychological stressor for the diagnosis of conversion disorder, but the current DSM-5 has eliminated that requirement for the diagnosis of all functional neurological symptom disorders, including PNES [1]. This change arose from the recognition that relevant psychological factors are often not demonstrable at the time of diagnosis and become apparent only during extensive psychotherapy, and that the failure to demonstrate such factors should not delay diagnosis or the initiation of treatment [1].

It can be especially difficult to elicit information regarding psychological stressors from patients with PNES and NEPS. They rate highly on scales of alexithymia (an inability to recognize or especially express one's own emotions verbally) and particularly low on scales of emotional awareness, even in comparison to other psychiatric patients [52]. Similarly, they rate higher on measures of avoidant behavior than matched patients with epilepsy, indicating a greater tendency to avoid unpleasant thoughts and internal stimuli [53]. These findings accord well with our experience that a large minority of patients with PNES deny being under any significant stress, no matter how stressful the life circumstances reported. As noted, pediatric patients with NEPS, similar to those with PNES only, are more likely than adults to have an acute life change as a psychological stressor, and less likely to have a history of abuse [45, 47, 48].

Semiology

The semiology of events can also inform clinicians' estimates of the probability of a psychogenic as opposed to epileptic etiology, with several important caveats. First, even events that are videotaped and directly reviewed by neurologists are accurately categorized as psychogenic versus epileptic in just 67–80% of cases on the basis of semiology alone [25]. Second, there is strong evidence that eyewitness reports of event semiology are unreliable and often inaccurate, specifically regarding characteristics distinguishing epileptic from psychogenic seizures [54]. Finally, frontal lobe epilepsy often presents with many of the semiologic features classically associated with PNES, including pelvic thrusting, opisthotonic posturing, bicycling movements, and asynchronous movements [55]. Focal dyscognitive seizures from a frontal lobe focus are usually very brief, so are less helpful in distinguishing SE from NEPS, but can easily be mistaken for intermittent PNES [56]. Frontal lobe epilepsy can be differentiated from PNES by ictal eye opening, occurrence from EEG-confirmed sleep, brief duration, tonic posturing, and stereotyped semiology [55, 57].

Semiologic characteristics consistently associated with psychogenic seizures include longer duration, e.g., convulsive seizures with motor components lasting longer than 2 min [19, 29, 38]. Psychogenic seizures are thought to not begin directly from EEG-confirmed sleep, but they frequently occur from "pseudosleep" which can easily be mistaken for true sleep by eyewitnesses without access to EEG [38, 58]. Asynchronous limb movements and pelvic thrusting are also consistently correlated with PNES as opposed to epileptic seizures—when frontal lobe epilepsy is excluded [29, 38, 58]. Importantly, pelvic thrusting is rare even in psychogenic seizures, with a poor sensitivity but good specificity for PNES [38, 58]. Side-to-side head or body movements and ictal crying have also been shown to have good specificity and fair sensitivity for psychogenic seizures [38, 58]. Vocalizations can occur at any time throughout psychogenic seizures and may be complex, with affective content, whereas vocalizations in generalized epileptic seizures (the "ictal cry") typically occur at onset and are simple and without affective content [37].

Eye closure during the ictal episode is strongly associated with PNES rather than epileptic seizures, with good sensitivity and specificity [38, 57, 58]. Intact recall for events during ictal unresponsiveness also has good sensitivity and specificity for PNES [38, 58]. Generalized tonic-clonic activity during an epileptic seizure typically declines gradually in frequency while increasing in amplitude over the course of the seizure. In contrast, convulsive activity in PNES tends to have a fluctuating course, with variable amplitude and an often unchanging frequency [58, 59].

Postictal confusion has good sensitivity and specificity for epileptic as opposed to psychogenic seizures [38, 58]. Histories of urinary incontinence and injury, though classically associated with epileptic seizures, have not been consistently shown to distinguish epileptic from psychogenic seizures [9, 38, 58].

Episodes consisting only of decreased responsiveness without motor activity (sometimes described as "swoon" or "catatonic" events) constitute a large minority of PNES, and prolonged episodes may be difficult or impossible to distinguish from nonconvulsive SE until an EEG is obtained [60]. Such events can generally be distinguished from cardiogenic syncope by their prolonged duration. Responsiveness to stimulation, resistance to eye opening, and self-protective maneuvers (when for example the patient's hand is dropped over his face) may suggest a psychogenic etiology [37]. Importantly though, many patients with NEPS may be entirely unresponsive even to noxious stimuli, and painful stimuli should not be used to diagnose or "break" catatonic NEPS. Rather, the diagnosis can be made easily and definitively by EEG (Table 4.1).

Electroencephalogram

The ILAE Nonepileptic Seizure Task Force has established criteria for "possible" and "probable" PNES relying only on event semiology and a nonepileptiform interictal EEG. The diagnosis of "clinically established" PNES requires visualization of a typical event (either in person or on video) by a clinician experienced in the diagnosis of epilepsy and separate non-video-EEG capture of a typical event without epileptiform abnormalities. The diagnosis of "documented" or definite PNES or NEPS requires video-EEG, interpreted by an experienced neurophysiologist, and allows a high degree of diagnostic certainty [37, 54]. The gold standard is capture of all typical episodes on video-EEG, without ictal EEG changes, and with normal awake EEG rhythms before, during, and after the event, in combination with a PNES-consistent clinical history and semiology [37]. During the event, the EEG may be obscured by artifact (Table 4.2).

There are important caveats in the use of EEG to diagnose PNES and NEPS. Scalp EEG has poor sensitivity (20–70%) for epileptiform activity in frontal lobe epilepsy [61] and in focal seizures without dyscognitive changes [62, 63]. For this reason, events that are clinically consistent with hypermotor frontal lobe seizures and simple partial seizures must be evaluated closely and considered seriously for epileptic etiologies even if video-EEG does not show epileptiform changes. As previously noted though, frontal lobe seizures are often very brief and therefore rarely a diagnostic consideration in the evaluation of potential SE. Simple partial SE can occur (including for example, *epilepsia partialis continua*, with ongoing involuntary focal motor activity without any alteration in consciousness) and is frequently without EEG abnormality, but any progression to impairment of consciousness should correlate with abnormalities on EEG. It is estimated that scalp EEG demonstrates diagnostic ictal or postictal features in >95% of focal dyscognitive seizures [64].

Conversely, it is important to avoid over-interpreting normal variants (e.g., wicket rhythm, rhythmic midtemporal theta of drowsiness, subclinical rhythmic electrographic discharges of adults (SREDA), positive occipital sharp transients of sleep, and nonspecific EEG abnormalities (e.g., nonfocal slowing) in patients being evaluated for SE versus

Table 4.1 Ictal characteristics of nonepileptic psychogenic status epilepticus versus focal dyscognitive or generalized convulsive status epilepticus

Seizure characteristics	Nonepileptic psychogenic status epilepticus	Status epilepticus
Onset	Gradual, from waking or "pseudosleep"	Abrupt, from waking or EEG-confirmed sleep
Movements	Asynchronous, pelvic thrusting, side-to-side thrashing, waxing and waning	Automatisms (in focal dyscognitive seizures); synchronous rhythmic movements, slowing in frequency and increasing in amplitude before stopping
Eyes	Eyes closed or fluttering	Eyes open, or with clonic blinking or nystagmus
Vocalization	Ictal crying, complex vocalizations with affective content	Repetitive simple speech (in focal dyscognitive); initial ictal grunt (with generalized convulsions)
Responsiveness	Waxes and wanes	Lost suddenly, regained gradually
Recall	Some retained memory of the event	No memory of the event
Postictal confusion	Rare	Common

EEG Electroencephalography

Table 4.2 Electroencephalography (EEG) of nonepileptic psychogenic status and generalized convulsive status epilepticus

EEG characteristics	Nonepileptic psychogenic status epilepticus	Status epilepticus
Interictal EEG	Normal or "not definitely epileptiform"	Often epileptiform
Ictal EEG	Normal; obscured by artifact	Epileptiform early; artifact obscures EEG during convulsion. Ictal rhythmic theta/delta activity
Postictal EEG	Normal, awake	Abnormal, focally slow (in focal dyscognitive); generally attenuated and then slow (in generalized convulsive)
Postictal recovery	Rapid, variable	Gradual, variable

NEPS. Nonspecific EEG abnormalities are common in both PNES and epilepsy [65], and the over-interpretation of nonspecific findings is one of the most common reasons for the misdiagnosis of patients as epileptic [66, 67]. Rather, specific epileptiform EEG changes (interictal spikes/polyspikes, sharp-and-slow waves; ictal rhythmicity and evolution; postictal focal or generalized slowing) should be identified to make a definite interpretation of epileptic seizures.

Other Tests

Although they are not necessary for the diagnosis of definite PNES or NEPS, there are other tests that may be useful in distinguishing between NEPS and SE, especially in the absence of EEG data. Elevated prolactin levels are highly specific (96%) for epileptic seizures, but sensitivity is best (60%) in generalized convulsive seizures, drops off in focal dyscognitive seizures (46%), and plummets in the setting of focal seizures without dyscognitive effects [38, 68]. The American Academy of Neurology (AAN) therefore classifies prolactin levels as a useful adjunct in differentiating generalized convulsive or focal dyscognitive epileptic seizures from PNES [68]. The AAN recommends that blood should be drawn 10–20 min after seizure onset and compared to a baseline non-ictal prolactin level, with a level at least twice normal suggestive of epileptic seizures. Importantly, prolactin has a short half-life, and its release may drop off during SE, resulting in a false negative if blood is drawn too long after seizure onset [69]. Use of dopamine agonists can also cause false negative results, while dopamine antagonists (and breast stimulation such as a suckling infant) can cause false positive results. Syncopal events may also raise prolactin levels [69].

Serum creatine kinase (CK) can also be used to distinguish between convulsive SE and NEPS, though its use has not been as extensively studied as that of prolactin [70]. CK levels usually elevate well above the normal range in patients with convulsive SE, while remaining within the normal range in patients with NEPS. Levels begin to elevate only 3 h after seizure onset, and remain elevated for approximately 36 h after cessation of seizures [70]. Serum cortisol, dexamethasone suppression tests, white blood counts, neuron-specific enolase, and brain-derived neurotrophic factor have not reliably distinguished between patients with NEPS and those with SE [37].

Structural neuroimaging has been only minimally useful in making the clinical distinction between epileptic and nonepileptic seizures. The majority of patients with epilepsy have normal magnetic resonance imaging (MRI) scans [71, 72], and a significant number of patients with PNES have incidental MRI abnormalities [72–74]. Functional neuroimaging studies have hinted at connectivity differences on a group level, but such techniques have not yet proven effective in distinguishing patients on an individual clinical basis [75].

Studies of personality measures such as the Minnesota Multiphasic Personality Inventory (MMPI) and MMPI-2 have suggested some differences in personality characteristics between patients with PNES and those with epileptic seizures but have failed to identify a single PNES personality profile and generally fail to show a combination of good sensitivity and specificity [76, 77]. Given that such assessments are time consuming and require the patient's extensive cooperation, they may be more useful for guiding therapy and for research purposes than for making the initial diagnosis of NEPS versus SE.

Differential Diagnosis of Status Epilepticus, Other than NEPS

In evaluating a case of potential SE or NEPS, other nonepileptic mimics of SE should be considered and excluded. These disorders can be conveniently subdivided between those that involve abnormal movements (and therefore mimic convulsive or focal motor SE) and those that involve only impaired responsiveness and therefore mimic nonconvulsive SE. Importantly, these disorders are more often encountered in critically ill patients in the ICU or in postoperative patients in the post-anesthesia care unit (PACU) than in newly presenting patients in the emergency department, whereas NEPS more often presents through the

emergency department in patients who are not otherwise acutely ill. Nevertheless, "non-NEPS" mimics of SE can potentially arise anywhere and must be considered whenever the diagnoses of SE and NEPS are contemplated.

Other Mimics of Generalized Convulsive or Focal Motor Status Epilepticus

The following "non-NEPS" mimics of SE can usually be easily clinically distinguished from convulsive or focal motor SE in the setting of preserved consciousness. They become more difficult to differentiate in patients who are obtunded or comatose, a common situation in the PACU and ICU. In the setting of altered consciousness, video-EEG has high sensitivity and can usually rule out an epileptic etiology [64] (Table 4.3).

Tremors, whether physiologic or acquired, can be prolonged and may mimic generalized convulsive or focal motor SE. Tremors tend to increase with stress and particular postures, may disappear with sleep, and are often associated with a family history of similar events [78]. Entrainment and distractibility can suggest a psychogenic etiology. Similarly, *shivering* can mimic clonic SE in the comatose patient. Changes in body temperature can be a clue to the diagnosis, but EEG may be required to make a definite diagnosis in comatose patients.

Dystonic reactions—fixed abnormal postures caused by sustained muscle contractions—can be caused by dopamine blocking agents (especially high potency typical neuroleptics such as haloperidol and fluphenazine but also atypical neuroleptics such as risperidone and pro-motility agents such as metoclopramide) as well as by tiagabine and other medications [79]. Oculogyric crisis is one type of dystonic reaction involving forced eye deviation and dyskinesias, lasting 20–30 min, and usually not associated with loss of consciousness [80]. *Decorticate and decerebrate rigidity or posturing can* result from hypoxic-ischemic injury and can mimic prolonged tonic seizures.

Table 4.3 Other mimics of convulsive or focal motor status epilepticus

Tremor
Shivering
Dystonia
Rigidity/posturing
Tetanus
Muscle spasms
Clonus
Myoclonus

Tetanus, or sustained muscular rigidity resulting from a toxin released by *Clostridium tetani*, can be generalized or localized, and classically begins with "locking" of the facial muscles followed by axial rigidity progressing to opisthotonic posturing. Voluntary movements can lead to repetitive "reflex spasms." *Tetany* caused by hypocalcemia or hyperventilation usually causes only brief contractions of the distal muscles in the hand but can rarely lead to prolonged carpo-pedal spasm mimicking focal dystonic SE in a patient who is comatose for other reasons [81].

Sustained *clonus* can result from either brain or spinal cord injury and can be inadvertently triggered or amplified by changes in posture or limb position. The temporal association with patient care maneuvers can offer a clue, but EEG may be necessary to definitively rule out clonic SE in the comatose patient. Both myoclonic status epilepticus and prolonged nonepileptic *myoclonus* occur in hypoxic-ischemic injuries due to cardiac or respiratory arrests, and EEG is usually necessary to differentiate the two.

Other Mimics of Nonconvulsive Status Epilepticus

The differential diagnosis for nonconvulsive SE is vast, in large part because the potential causes of encephalopathy in the hospitalized patient are so numerous. Fortunately, nonconvulsive SE can generally be ruled out by 24 h of video-EEG monitoring [82]. Besides NEPS, the following items should be considered as alternative diagnoses (Table 4.4).

Toxic-metabolic encephalopathy is the most common and broadest category on the differential diagnosis of nonconvulsive SE. In encephalopathies of all etiologies, the EEG may show diffuse slowing and, in more severe cases, generalized rhythmic delta activity (GRDA) and generalized rhythmic discharges with triphasic morphology, but focal or clearly epileptiform abnormalities should call the diagnosis into question. Neuroimaging should show no new focal abnormalities.

Septic encephalopathy is the single most common cause of acute toxic-metabolic encephalopathy in adults and is thought to be caused by inflammatory cytokines, reductions in monoamine neurotransmitters, and altered blood–brain barrier permeability [83]. *Metabolic* causes may include hepatic encephalopathy, uremia, Wernicke's encephalopathy (dysfunction of central gray structures due to thiamine deficiency), hypercarbic respiratory failure, hyponatremia, hypernatremia, hypocalcemia, hypercalcemia, hypoglycemia, hyperosmolar hyperglycemia, or diabetic ketoacidosis. *Toxic encephalopathies* can include intoxication with (or in many cases, withdrawal from) benzodiazepines, barbiturates, anticholinergics, antihistamines, opioids, neuroleptics, SSRIs or other antidepressants,

Table 4.4 Other mimics of nonconvulsive status epilepticus

Toxic-metabolic encephalopathy
Septic encephalopathy
Metabolic encephalopathies (hepatic encephalopathy, uremia, Wernicke's encephalopathy, hypercarbic respiratory failure, hypoxic-ischemic encephalopathy, hyponatremia, hypernatremia, hypercalcemia, hypocalcemia, hypoglycemia, hyperosmolar hyperglycemia, diabetic ketoacidosis)
Toxic encephalopathies/drug effect (benzodiazepines, barbiturates, anticholinergics, antihistamines, opioids, neuroleptics, SSRIs or other antidepressants, antispasmodics, antiemetics, interferons, street drugs, alcohol)
Encephalitis
Locked-in state
Akinetic mutism
Severe Parkinsonism
Stiff-person syndrome
Psychiatric and behavioral episodes (catatonia, self-stimulation)
Kleine–Levin syndrome

antispasmodics, antiemetics, interferons, street drugs (cocaine, lysergic acid diethylamide, phencyclidine, methylenedioxyme diamphetamine, mescaline, psilocybin), and most commonly, alcohol.

Encephalitides can result in both epileptic seizures and behavioral changes that can be easily mistaken for nonconvulsive SE. Two specific examples are worthy of mention. *Herpes simplex encephalitis* is a viral infection most commonly affecting the frontotemporal structures and causing fever, headache, focal deficits (including superior visual field cuts, aphasia, or hemiparesis), and focal or generalized seizures. Even in the absence of seizures, patients may be confused and unable to form memories, have complex automatisms, and behave inappropriately [84]. The EEG may show frontotemporal sharp waves or lateralized periodic discharges, and MRI may show hemorrhagic frontotemporal lesions. *Paraneoplastic and autoimmune limbic encephalitis* may also cause both epileptic seizures and behavioral changes mimicking nonconvulsive SE, including memory formation problems, emotional lability, personality change, depression, and anxiety [85].

Locked-in syndrome refers to quadriplegia and anarthria with preserved consciousness, caused by injury to motor tracts in the brainstem. It is classically associated with central pontine myelinolysis but is in fact most frequently caused by anterior pontine infarction or hemorrhage [86]. The patient may have control only over eye opening or closing or vertical eye movements, or combinations of these. The EEG may be entirely normal or show only nonspecific generalized slowing or focal or multifocal slowing in patients with vascular disease. *Akinetic mutism is* a condition in which the patient is awake but unable to respond due to extreme abulia or lack of motivation, and is caused most frequently by mesiofrontal lesions such as anterior communicating artery aneurysm rupture, bilateral thalamic strokes, or bifrontal neoplasms, though medications are another possible cause. Neuroimaging demonstrating a focal lesion is key to the diagnosis of both conditions. *Severe Parkinsonism* can result in patients who appear entirely catatonic due to extreme rigidity and bradykinesia but may respond positively to levodopa. *Stiff-person syndrome* can also cause apparent unresponsiveness due to severe rigidity, in association with autonomic instability, with anti-glutamic acid decarboxylase antibodies in 60% of patients [87].

Other psychiatric and behavioral episodes besides NEPS may present with prolonged episodes of decreased responsiveness mimicking nonconvulsive SE. Catatonia occurs in the setting of an underlying severe psychiatric or medical disorder and is marked by immobility and mutism, often associated with negativism (resisting instructions or attempts to move the patient), waxy flexibility, posturing, and echolalia (repetition of another's speech), echopraxia (repetition of another's movements), and a positive response to benzodiazepines [88]. *Self-stimulation* in young children or in mentally retarded populations can present with prolonged rocking, swaying, or chewing movements accompanied by a dazed appearance. *Kleine–Levin syndrome* is a rare sleep disorder, primarily affecting adolescent males, characterized by episodes of severe hypersomnia associated with confusion, derealization, compulsive eating, and hypersexuality [89]. Episodes last days to weeks and are separated by months of normal behavior and sleep.

Treatment of NEPS

Once the definite diagnosis of NEPS has been made and epileptic seizures are ruled out, the first step of treatment is presentation of the diagnosis to the patient. Making and clearly delivering a positive diagnosis in a timely manner is

important for the patient's long-term prognosis and to minimize repeated and unnecessary use of healthcare resources [11, 90, 91]. This is one of the key tasks of the neurologist and must be performed in a supportive and nonjudgmental manner so as to facilitate adherence with the next stage of psychotherapeutic treatment. This may decrease the chances of repeated appearances in other emergency departments [92, 93].

Formal validated protocols for delivering the diagnosis of PNES are available [94, 95]. The key points are to acknowledge that the events are real and disabling, to give a positive diagnosis with a name for the condition, to explain that it is a common and recognized condition, to describe the psychological causes (stress, strong affect), to specify that it is not epilepsy and that anti-seizure drugs are not effective, to explain that psychological treatment is effective, to discuss referral to a behavioral health specialist, and to reassure the patient that improvement can be expected and complete resolution is possible [94]. We have also found it helpful to make comparisons with more commonly experienced responses to extreme stress, such as tachycardia, diaphoresis, and panic attacks.

If at all possible, behavioral health specialists should be involved in the early evaluation of the NEPS patient and in delivering the diagnosis to the patient [96]. This facilitates evaluation for common psychiatric comorbidities and suicidal or parasuicidal behavior (i.e., suicidal "gestures" unlikely to result in death, such as cutting) and helps present a single unified team to the patient, thus reducing the sense of being abandoned by neurologists and dismissed to psychiatrists. Patients with PNES have consistently poor adherence with psychotherapy, and one study showed that adherence is significantly improved when the referral happens within a single unified system rather than to an outside mental health specialist [97]. Introducing behavioral health specialists early allows them to use the NEPS episode as a teachable moment, motivating future psychotherapy. If mental health clinicians cannot be involved prior to delivery of the diagnosis, they should be involved as soon afterwards as possible. It is vitally important that there be clear and open communication between the referring neurologist and the behavioral health specialist (as well as the primary care physician) regarding the diagnosis and the basis on which it was made.

If epileptic seizures are entirely ruled out, another important early step is to stop all anti-seizure drugs (ASD), except those providing a documented psychopharmacologic benefit to the patient. A randomized controlled trial of immediate versus delayed withdrawal of ASDs in patients with newly diagnosed PNES showed improved outcome with fewer subsequent seizure-like events, less use of rescue medicines, and improved locus of control in the immediate withdrawal group ("locus of control" refers to individuals' belief that they can control events affecting them) [98]. Stopping ASDs while the patient remains on video-EEG also allows the clinical team to evaluate for new interictal epileptiform abnormalities or epileptic seizures emerging in the absence of medications. If possible, we recommend allowing patients with newly diagnosed NEPS to remain hospitalized for at least 1 day after the diagnosis is made, to allow the withdrawal of medications, to allow patients to absorb the diagnosis, and to foster relations with the neurologists and mental health clinicians who will follow them as outpatients.

A minority of patients may experience resolution of PNES with no intervention beyond the delivery of the diagnosis, with 13–16% of patients becoming seizure free at a 6–12 month follow-up [99, 100], but the large majority of patients require further treatment. The best-studied treatment modality is cognitive behavioral therapy (CBT)-based psychotherapy, which has been shown to reduce seizure frequency and improve quality of life in two pilot randomized controlled trials [101, 102]. Other therapeutic modalities, including psychodynamic interpersonal therapy, have been shown to be effective in observational studies [100, 103, 104]. Psychopharmacologic agents such as SSRIs or neuroleptics may be indicated to treat comorbid psychiatric disorders but have not thus far been demonstrated to be effective in treating PNES directly [103]. There are no studies specifically regarding treatment of NEPS.

The proper role of the neurologist in treatment of PNES and NEPS following the delivery of the diagnosis remains controversial. In a survey of epilepsy experts at level 4 epilepsy centers across the United States, a minority advocated no neurologic follow-up but only a referral to behavioral health specialists [105]. The majority of experts recommend some outpatient neurologic follow-up. Our recommendation is that outpatient neurologic follow-up should continue until anti-seizure medications are removed and until care is established with a mental health specialist comfortable with providing treatment for functional neurological symptom disorders, as well as with a primary care doctor capable of evaluating and, if necessary, appropriately referring future psychogenic complaints. At that point, the outpatient neurologist can follow on an as-needed basis, with the patient referred back in the event of new seizure semiology or other apparently neurologic complaints that the behavioral health specialist and primary care physician are uncomfortable evaluating. Open communication about the basis for the diagnosis of PNES and neurologists' ongoing availability can help reassure other clinicians and minimize unnecessary additional tests and evaluations. Patients with

mixed PNES and epileptic seizures will likely need to continue anti-seizure medications and outpatient neurologic follow-up indefinitely.

Prognosis of NEPS

Historically, 75% of patients with PNES continue to have seizures and associated disability when followed up 5–10 years after diagnosis [9, 12, 13]. At 4 years after withdrawal of all anti-seizure medications, 40% of patients are again taking such medications [9]. Duration of illness is thought to be a prognostic marker, with shorter duration, especially <1 year, associated with improved outcomes [90].

The generally poor long-term outcomes for PNES and NEPS may improve in the coming years, as time from symptom onset to diagnosis becomes shorter and as CBT-based psychotherapy becomes more widely utilized. Improving education of clinicians regarding PNES and NEPS may also be of benefit. Nevertheless, many obstacles to effective treatment remain: these include poor communication between diagnosing neurologists and treating mental health specialists, insufficient numbers of behavioral health clinicians comfortable in treating functional neurological symptom disorders, bias against patients perceived as deliberately "faking" their episodes, and non-adherence with treatment. Patients with PNES and NEPS have repeatedly demonstrated high dropout rates (50% and higher) following the diagnosis, during the referral to psychotherapy, and during the prescribed psychotherapy regimen [97, 102, 106, 107]. Two strategies that appear to result in better adherence include referring patients to therapy within a unified health system and involving family members or close friends in the diagnostic and treatment processes [97, 106].

Future Research

Prospective research in the subpopulation of patients with NEPS is difficult and rare. Data about the diagnosis, treatment, and prognosis of PNES is often presumed to apply equally to NEPS because studies have failed to identify consistent differences in medical history, psychiatric history, or personality characteristics. There is some reason to worry that patients with NEPS (presenting more frequently through the emergency department rather than the EMU) may have worse adherence with therapy, response to treatment, and long-term prognosis than other patients with PNES. Prospective studies of patients with NEPS, evaluating their response to psychotherapy and long-term outcomes, are urgently needed. Such research might guide targeted intensive interventions, potentially including even inpatient or partial hospitalization psychiatric treatment, to patients with especially poor prognoses.

Additional areas of needed research include: (1) programs to transition patients with NEPS from the emergency department where they often present to longitudinal care with neurologists and behavioral health specialists; (2) evaluation of the optimal duration of hospitalization at the time of diagnosis of NEPS; (3) training curricula to familiarize medical students and residents with NEPS and other functional neurological symptom disorders; and (4) interventions to improve the common problem of non-adherence with treatment among patients with NEPS. Motivational interviewing (MI) is "a person-centered counseling style" originally developed to decrease risky alcohol consumption but has since been used successfully for such varied purposes as promoting weight loss among obese patients and increasing adherence to antiretroviral therapy among patients with HIV infection [108–111]. A randomized trial of MI is currently underway at our institution to improve adherence with therapy among patients with PNES and NEPS.

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Periodic EEG Patterns

5

Jonah Grossman and Brandon Foreman

Introduction

Periodic and rhythmic electroencephalography (EEG) patterns are encountered commonly with the increased use of continuous EEG (C-EEG) in the hospital and intensive care unit. These patterns were initially identified over 60 years ago and have been described in association with a variety of pathologies: ischemic stroke, encephalitis, post-anoxic cortical injury, multi-organ failure, drug toxicities, and anesthetic withdrawal. The clinical implications of periodic or rhythmic discharges differ based on their underlying cause; no unifying pathophysiology has been uncovered for their appearance. Periodic and rhythmic discharges are often found during recordings from patients with impaired mental status or other clinical symptoms concerning for nonconvulsive seizures, such as staring, periodic or rhythmic eye blinking, mutism, facial twitching, automatisms, asterixis, or subtle myoclonic movements [1–3]. In some of these cases, periodic or rhythmic discharges are viewed as lying more on the ictal rather than the interictal end of the ictal-interictal continuum. Nevertheless, the clinical management of rhythmic or periodic discharges remains a matter of debate, largely because it may be difficult to discern where along this spectrum a particular patient lies.

Terminology

In 2012, the American Clinical Neurophysiology Society (ACNS) provided updated, standardized terminology to describe patterns encountered during C-EEG monitoring [4]. Two main terms describe the morphology and location of the patterns discussed in this chapter. Main Term 1 describes *location* as lateralized, generalized, bilateral independent, or multifocal. Main Term 2 describes *morphology* as rhythmic, periodic, or spike-and-wave. *Periodic discharges* are defined as waveforms with a relatively uniform appearance that repeat at nearly regular, quantifiable inter-discharge intervals (Fig. 5.1a). *Rhythmic discharges* are defined as relatively uniform discharges that recur *without* an inter-discharge interval (Fig. 5.1b). In a validation study of the standardized ACNS terminology, the percent agreement and inter-rater reliability of Main Terms 1 and 2 were 91.3% ($\kappa = 0.89$) and 85.2% ($\kappa = 0.8$), respectively [5]. Many of the terms used in the literature, such as "periodic lateralized epileptiform discharges (PLEDs)" have been updated, and importantly, terms such as "epileptiform" have been avoided to reduce bias in the interpretation and reporting of these patterns. For the purposes of this chapter, the term *ictal* will be used to refer to any clinical event or EEG pattern thought to represent a true underlying epileptic pathology, whether convulsive or nonconvulsive. Table 5.1 contrasts commonly encountered terminology with the preferred, standardized terminology that will be used hereafter.

Periodic Discharges: Pathophysiology

Periodic discharges (PD) are thought to represent synchronized, aberrant firing of dysfunctional populations of cortical neurons with prolonged recovery times, or refractory periods, analogous to that observed after the paroxysmal depolarizing shift that characterizes epileptiform discharges [6–8]. In a model of the hippocampal CA3 region, spontaneous excitatory postsynaptic potentials (EPSPs) trigger neuronal bursting by depolarization of postsynaptic neurons in an excitable post-refractory state or even (if the quantity of EPSPs is great enough) neurons still in a refractory state [9]. Decreased interneuronal inhibition of adjacent neuronal column coupling, resulting in excess excitation, may result from frequent

J. Grossman · B. Foreman (✉)
Department of Neurology & Rehabilitation Medicine, Division of Neurocritical Care, University of Cincinnati Medical Center, 231 Albert Sabin Way, ML0517Cincinnati, OH 45267, USA
e-mail: brandon.foreman@uc.edu

J. Grossman
e-mail: grossmjb@ucmail.uc.edu

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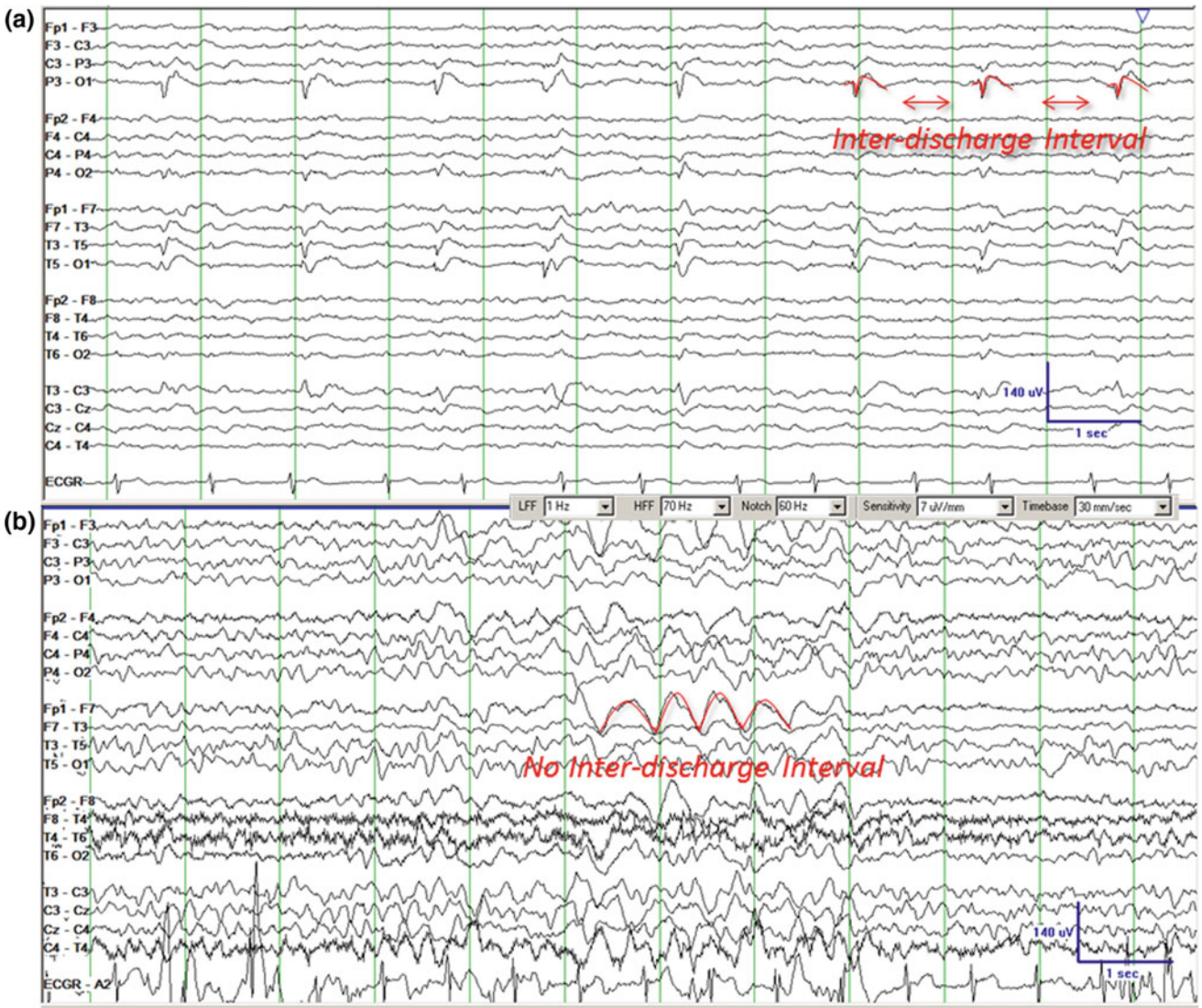


Fig. 5.1 Examples of periodic and rhythmic waveforms. EEG is displayed in a longitudinal bipolar montage. Filter settings and scale are shown in the figure. **a** *Left* temporoparietal lateralized periodic discharges occurring at 0.5–1 Hz. Note the regular recurrence of waveforms that appear similar in morphology, and a measurable inter-discharge interval. **b** Frontally predominant generalized rhythmic delta at approximately 2 Hz in a very brief (<10 s) run. Note again a regular recurrence of similar appearing waveforms. Rhythmic discharges are characterized by a lack of an inter-discharge interval

depolarizations [10] and manifest as periodic, phase-locked, super-positioned bursts [11]. By contrast, increased *inhibitory* tone may make otherwise continuous ictal activity appear periodic [12]. In cortical slice models, a silent interval between discharges has been associated with discharge-induced extracellular alkalization and potassium concentrations with intracellular acidification, inhibiting synchronized neuronal firing by uncoupling gap junctions. Interestingly, when the intracellular acidification was prevented, periodicity was replaced with continuous ictal activity [13]. More recently, the observed spatial dynamics of ictal discharges suggest that small cortical areas of tonic firing (termed the ictal wavefront) generate much larger regions of synchronized, rhythmic discharges distinct from the source of ictal activity [14, 15] and that these lower frequency discharges counterintuitively reflect *desynchronized* neuronal bursting and eventual seizure termination. For this reason, periodic discharges may be recorded on scalp EEG as a result of either multifocal or aberrantly propagating ictal wavefronts, or as a result of increasing refractoriness to a persistent ictal focus. Evidence exists that smaller foci of ictal activity may underlie surface EEG that demonstrates only interictal, periodic, or rhythmic discharges (Fig. 5.2) [16, 17].

Periodic or rhythmic discharges in some cases may not be ictal, but a manifestation of neuronal death [18, 19] or of an anatomic disconnection between cortical and subcortical

Table 5.1 Updated terminology for periodic and rhythmic discharges

Commonly Used Terminology	Standardized ACNS terminology
Periodic lateralized epileptiform discharges (PLEDs)	Lateralized periodic discharges (LPDs)
PLEDs+	LPDs+, with modifiers +F for superimposed faster frequencies or +R for superimposed rhythmic frequencies
Generalized periodic epileptiform discharges (GPEDs)	Generalized periodic discharges (GPDs)
Triphasic waves	GPDs with triphasic morphology
Bilateral independent periodic lateralized epileptiform discharges (BIPLEDs)	Bilateral independent periodic discharges (BIPDs)
Frontally predominant intermittent rhythmic delta activity (FIRDA)	Frontally predominant generalized rhythmic delta activity (GRDA)
Stimulus-induced rhythmic, periodic, or ictal discharges (SIRPIDs) with focal rhythmic delta activity	Stimulus-induced lateralized rhythmic delta activity (SI-LRDA)

ACNS American Clinical Neurophysiology Society
Adapted from Hirsch et al. [4]

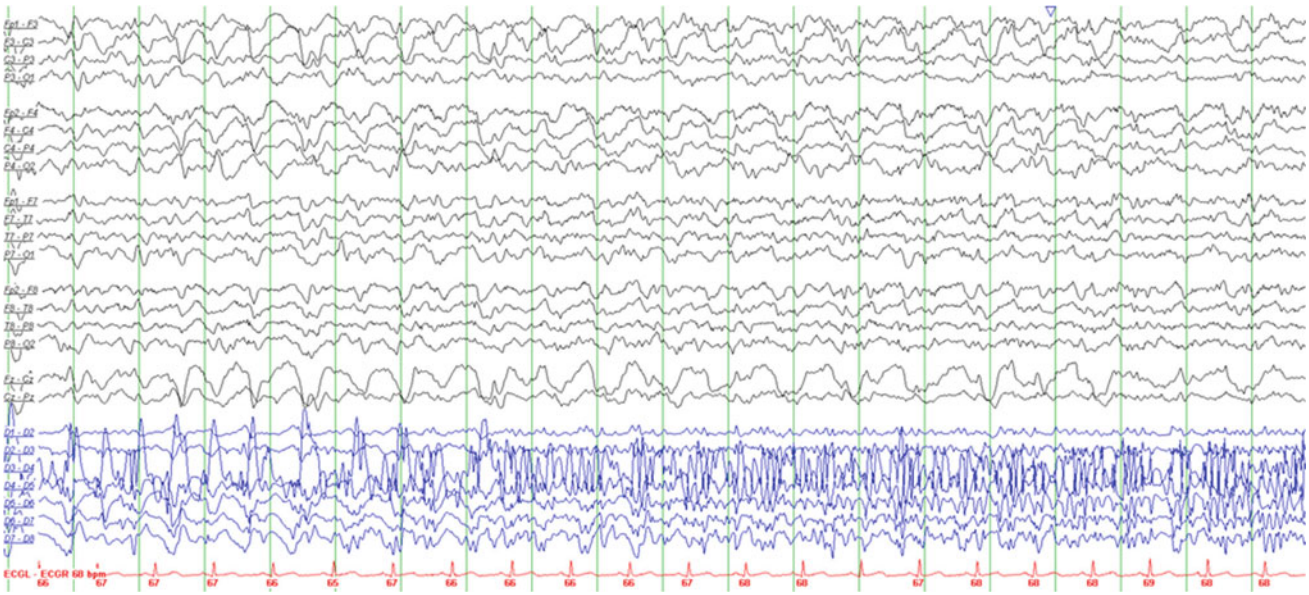


Fig. 5.2 Example of cortical seizure seen as generalized rhythmic delta on surface EEG. 44-year-old man with respiratory arrest and asystole who presented in coma with myoclonic jerking movements. An invasive cortical electrode was placed for multimodal neuromonitoring. Surface or scalp EEG is displayed in a longitudinal bipolar montage (*black waveforms*), and depth electrode recordings are displayed in a bipolar montage (*blue waveforms*), with D1 representing the deepest contact, and D8 representing the most superficial contact. The depth recording demonstrates an evolving ictal theta-alpha pattern with spread into neighboring electrodes, while the scalp EEG reflects 1–1.5 Hz generalized rhythmic delta. Low frequency filter set at 1 Hz; high frequency filter set at 70 Hz; the sensitivity of the scalp recording is set at 7 uV/mm, depth recording at 15 uV/mm

regions [5], both of which create conditions for abnormally synchronous cortical oscillations and may contribute to cortical hyperexcitability. Animal studies have demonstrated that while the application of excitatory substances to intact cortex produces irregular rhythmic bursts, much more regular rhythmic bursts occur with thalamectomized cortex [20]. Moreover, nearly regular periodic bursts with interburst suppression are seen upon stimulation of completely undercut perfused cortex. In humans, one case-control study found radiographic evidence of white matter changes and subcortical atrophy (but not cortical atrophy) associated with encephalopathy and generalized periodic discharges with triphasic morphology [21]. Autopsy-based studies, however, have demonstrated that periodic discharges may be recorded distant to a pathologic lesion or from intact cortex [22]. After generalized convulsive status epilepticus (GCSE), periodic discharges are often observed on an attenuated background [23, 24], and others have suggested that periodic discharges

particularly represent a "fatigued" state of clonic firing [25]. Periodic discharges have also been recorded in ischemic penumbra of animals undergoing occlusion of the middle cerebral artery [26]; contralateral to the occlusion, rhythmic delta activity was observed, suggesting that periodic and rhythmic discharges reflect broader changes in the balance between inhibition and excitation. Whether periodic discharges reflect aberrant ictal activity or an alteration in inhibitory and excitatory cortical inputs, cortical dysfunction remains the common denominator. Direct cortical injury, such as hypoxia, or widespread metabolic dysfunction, such as acute hepatic failure, may equally result in a similar EEG phenotype, a concept reflected in the term "interictal-ictal continuum," used to describe periodic or rhythmic patterns that may or not be ictal depending on their complex, underlying contributors [27].

Periodic Discharges: Implications for Seizure Detection

Both periodic and rhythmic discharges are highly associated with the development of clear, unequivocal seizures. In a retrospective analysis of 625 consecutive hospitalized patients undergoing >18 h of C-EEG, periodic discharges were recorded during the first 30 min in 10% (60/625) of patients, 27% (16/60) of whom had a seizure at some point thereafter [28]. Of 570 hospitalized patients undergoing C-EEG, lateralized periodic discharges (LPDs) were associated with seizures only after >24 h of monitoring, with an odds ratio of 3.1 [29], while in a case-control study of generalized periodic discharges (GPDs), only those with GPDs exhibited seizures after >48 h of monitoring compared with controls without GPDs [30]. Currently, guidelines from the Neurocritical Care Society recommend at least 48 h of C-EEG for comatose patients to rule out NCSE [31]. A 2010 survey found that the majority of adult and pediatric neurologists would monitor C-EEG in patients with periodic discharges for >24 h (40% for 24 h, 29% for 48 h, and 15% for 72 h) [32]. We recommend up to 48 h of C-EEG for all hospitalized patients with newly diagnosed periodic or rhythmic discharges where resources are available. Where C-EEG is not available, we recommend repeated EEG evaluation for patients with periodic or rhythmic discharges who exhibit intermittent or persistent changes in neurologic examination.

Lateralized Periodic Discharges (LPDs): Incidence and Association with Seizures

Focal or multifocal regions of periodic discharges are termed LPDs, bilateral independent periodic discharges (BIPDs), or multifocal periodic discharges (MfPDs). LPDs were initially described as repetitive, lateralized, spike- or sharp-wave complexes followed by a slow-wave and lasting from 0.3 to 2 s with repetition rates of 0.2 to 3 Hz [22, 25, 27, 33]. LPDs may be focal or spread broadly over one hemisphere, sometimes with extension to the homologous area on the contralateral side (albeit to a lesser extent). Most often, LPDs and BIPDs have maximum voltage in the frontocentral regions [34]. LPDs tend to vary from patient to patient in their periodicity (0.5–4 s) [27], morphology (e.g., biphasic, triphasic, or polyphasic spike- and sharp-waves) [35], voltage (50–300 μV), and duration (60–1000 ms) [36]. LPDs do not always exist continuously over the entirety of a recording, although LPDs have persisted for months and even years [33, 37, 38]. More commonly, LPDs dissipate between 9 and 16 days (range 1–31 days) after clinical symptom onset, even in the face of progressive neurologic disease (e.g., progressive brain tumor) [22, 25, 33, 39]. Their natural progression proceeds with decreasing frequency, prolongation of discharge duration, and evolution to paroxysmal delta and finally theta frequency slowing [33].

LPDs have been described in 0.4–1% of routine EEGs [27] and in 6–22% of C-EEG series [29, 40, 41]. Clinically, LPDs are often accompanied by focal neurologic deficits and alterations in mental status [33]. LPDs may be the electrographic correlate of focal seizures, such as *epilepsia partialis continua* [42], focal sensory-motor seizures [43], or complex partial seizures [22, 33, 44]. More often, LPDs occur in association with an acute or subacute focal neurologic disease, usually involving the cortex, capable of generating symptoms independent of LPDs [38, 45]. Table 5.2 lists etiologies associated with LPDs [22, 25, 33, 35–38, 45–64]. The most common etiology underlying LPDs is ischemic stroke [22, 33, 35, 65, 66]. In a meta-analysis of 586 patients from several earlier studies of LPDs (1964–1987), 35% had a primary etiology of ischemic stroke [25]. Interestingly, one in ten had a metabolic etiology, suggesting a role for metabolic stressors in lowering the threshold for LPDs to develop in much the same way that the seizure threshold may be lowered in patients with epilepsy. Studies utilizing C-EEG have confirmed that one-quarter have remote or progressive brain disease [67]. Some have focused on specific disease processes: LPDs were seen in 13% of those with intracerebral hemorrhage (ICH), particularly when bleeding was closer to the cortex (<1 mm) and when ICH was greater than 60 cc 24–72 h post-bleed, and less frequently in the presence of midline shift 3–7 days post-bleed [68]. LPDs were also observed in 20% of those with subarachnoid hemorrhage (SAH) [69]. Within 24–48 h of suspected herpes simplex encephalitis, LPDs were observed in 90% with positive HSV PCRs (at symptom onset) and 30% with negative HSV PCRs; the sensitivity of EEG decreased after 48 h [70]. Even cohorts of patients undergoing C-EEG may under-estimate the frequency of periodic discharges in

Table 5.2 Etiologies of lateralized periodic discharges [22, 25, 33, 35–38, 45–64]

Category	Etiology
Neurovascular	Ischemic infarct (arterial occlusion, watershed infarct, global anoxic ischemic injury, neonatal encephalopathy, sickle cell disease) Intracerebral hemorrhage (acute or remote) Cerebral venous occlusion Subarachnoid hemorrhage (acute or remote) Periarteritis nodosa Arterio-venous malformation Angioma Carotid endarterectomy, carotid stenting Posterior reversible encephalopathy syndrome Mitochondrial encephalopathy with lactic acidosis and stroke-like episodes (MELAS)
Space occupying lesion, malignancy	Tumor (primary, metastatic) Abscess Cystic lesion Carcinomatous meningitis
Infection, inflammation, autoimmune	Viral encephalitis (Epstein–Barr virus, influenza B, cytomegalovirus, Japanese encephalitis) Necrotizing encephalitis (herpes simplex virus) Bacterial meningitis Bacterial cerebritis Neurocysticercosis Behçet disease Paraneoplastic encephalitis Multiple sclerosis Neurosyphillis Rasumussen encephalitis Tuberculoma, tuberculous meningitis or vasculitis Post-vaccinal encephalomyelitis Encephalomalacia Anti-NMDAR, anti-Hu, VGKC complex/LGI1-antibody encephalitides Central nervous system toxoplasmosis Acute disseminated encephalomyelitis
Trauma	Head trauma (acute or remote), contusion Subdural hematoma Post-craniotomy
Systemic Illness	Electrolyte imbalance (hypo/hyperglycemia, hypo/hypercalcemia, hypo/hypernatremia, hyper/hypokalemia, hypomagnesemia) Alcohol intoxication/alcohol-related seizures Alcohol/benzodiazepine withdrawal Hypertensive encephalopathy, eclampsia Syndrome of inappropriate anti-diuretic hormone SIRS, sepsis, fever, or acidosis Deep hypothermia Hepatic encephalopathy Hypothyroidism Hyperosmolar non-ketotic state Reye syndrome Iatrogenic (i.e., aminophylline)
Epilepsy	Cortical dysplasia Tuberous sclerosis Postictal Post-electroconvulsive therapy Chronic ipsilateral perinatal hemorrhage with cerebral palsy Leukodystrophy Idiopathic epilepsy
Migraine	Migraine with aura Familial hemiplegic migraine
Degenerative	Creutzfeldt–Jakob disease

NMDAR N-methyl-D-aspartate receptor
VGKC voltage-gated potassium channel
LGI1 leucine-rich, glioma inactivated 1
SIRS systemic inflammatory response syndrome

those with critical neurologic illness such as traumatic brain injury or subarachnoid hemorrhage, because scalp EEG recordings can miss some focal periodic discharges seen only on direct cortical recordings [16, 17]. For instance, in a series of patients with traumatic brain injury (TBI), 38.2% (13/34) had periodic discharges recorded during electrocorticography, of whom 8/13 had no periodic discharges on surface EEG [17].

LPDs are frequently associated with seizures, found in 49–90% of patients with LPDs [25, 27, 46], although in many studies using routine EEG, recordings were not made until a seizure was suspected clinically, likely enriching the cohort of patients with LPDs to include those at highest risk for seizures. In more recent C-EEG series, 27–49% of those with LPDs on C-EEG developed seizures [28, 29, 40]. The addition of "plus" characteristics (superimposed faster frequencies or rhythmic waveforms in conjunction with LPDs) increases the risk for seizures. LPDs+ account for between 17 and 60% of all LPDs, and LPDs+ and BIPDs+ are associated with seizures in 85 and 100% of cases, respectively, [36, 46].

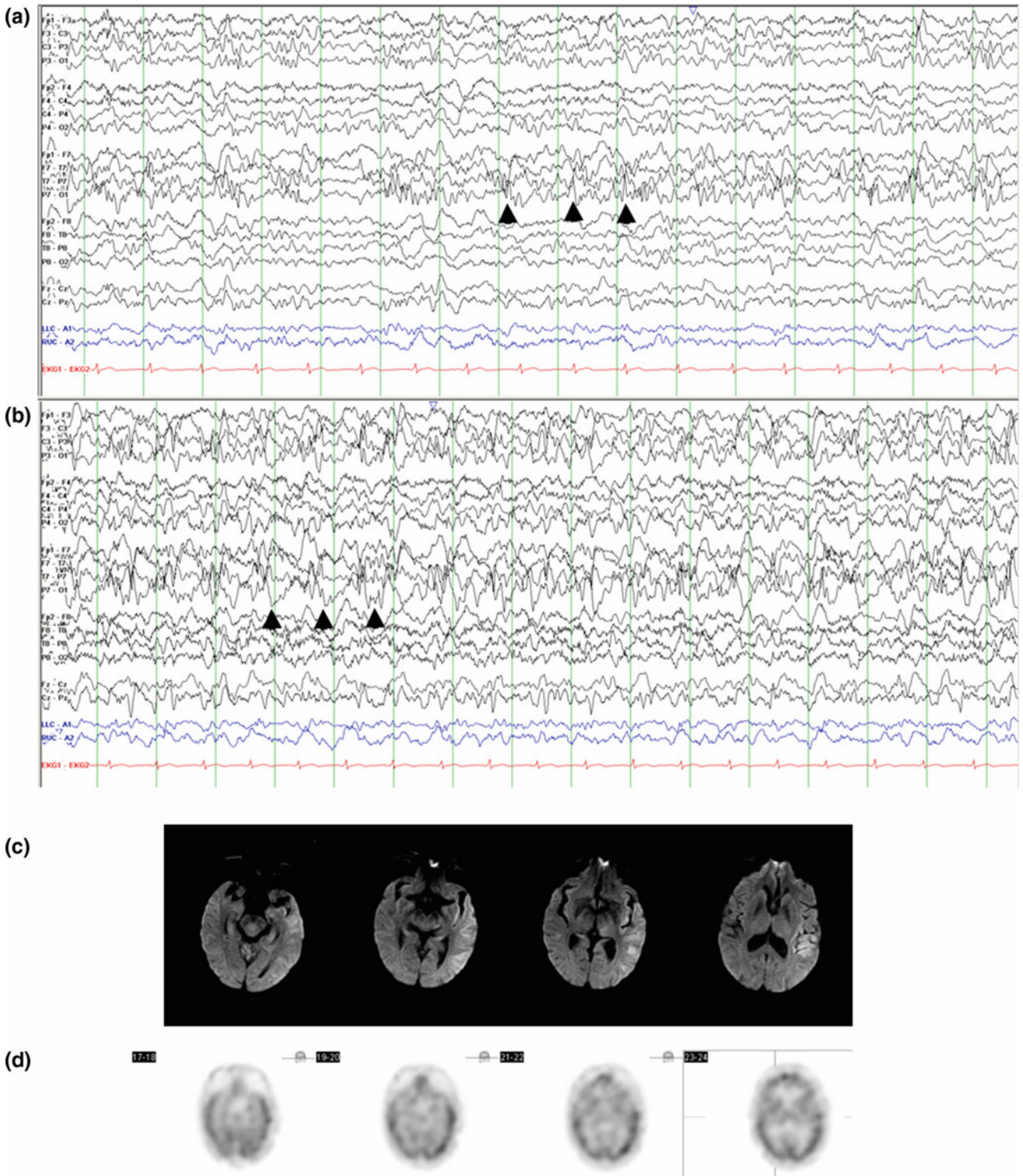
Lateralized Periodic Discharges: Prognosis

LPDs have been associated with increased morbidity and mortality. The overall mortality in adult patients with LPDs of any etiology ranges from 27 to 52% [25, 47, 71]. In two separate studies of patients being treated for status epilepticus (SE), LPDs were significantly associated with death or poor outcome [71, 72] and the presence of LPDs increases the odds that SE will become refractory [73]. After SAH, the presence of LPDs increases the odds for poor outcome by a factor of 18.8 after adjusting for age and disease severity; after ICH, the odds ratio for poor outcome increases to 11.9 [68, 69]. Some have suggested that an acute etiology underlying LPDs serves as a key determinant of outcome [34], but a case-control study of 37 patients with LPDs *without* acute brain injury compared with age- and etiology-matched controls found LPDs were independently associated with functional decline [67]. Another case-control series of LDPs, BIPDs, and GPDs found an independent association with death or disability, along with age and liver dysfunction, with a dose effect suggestive of increasing morbidity with increasing discharge burden [74]. Nevertheless, the duration of discharges does not appear to predict condition at discharge (following commands, vegetative or deceased) in patients admitted to a neurointensive care unit, even if periodic discharges continue for five or more consecutive days [39].

Lateralized Periodic Discharges: Diagnostic Approaches

Evidence is lacking that LPDs independently create harm sufficient to warrant aggressive management in ***all*** cases. Thus, management of LPDs requires an individual approach in order to stratify the effect of LPDs on a given patient. Seizures, both convulsive and nonconvulsive, demonstrate clear adverse effects on both the brain and the body [75, 76] and the first point of distinction rests on whether an LPD pattern represents ictal activity. Proposed definitions of nonconvulsive seizures based on EEG include periodic discharges with a frequency >2.5 Hz [77]. LPDs with clinical seizure activity, e.g., contralateral hand twitching, are unequivocally ictal [12, 37, 41] regardless of the frequency of the LPDs. Interestingly, LPDs with a clear clinical correlate occur more often when the LPDs arise near motor cortex [41] suggesting that LPDs arising more broadly or from less eloquent areas may still be ictal despite a lack of clear clinical correlate. This is supported by studies that have demonstrated LPDs in association with FDG-PET hypermetabolism or SPECT hyperperfusion, physiologic changes expected during an ictal study in patients with epilepsy [43, 78–81]. For instance, in a series of patients undergoing workup for focal SE, three exhibited LPDs with hypermetabolic regions concordant with the region of LPD activity [80]. Other methods of determining regions of hyperperfusion include susceptibility weighted or arterial spin labeling MRI sequences [82, 83]. After traumatic brain injury, periodic discharges recorded in the cortex and on scalp EEG have been shown to create metabolic crises by increasing demand relative to supply, leading to increases in the lactate to pyruvate ratio on cerebral microdialysis [17]. In certain other populations, such as trauma, focal vascular stenosis, or deep barbiturate coma, hypermetabolism or hyperperfusion may be difficult to interpret or unreliable without carefully comparing pre- and post-treatment imaging for a given patient [81].

Both hyperemia and supply–demand mismatch may result in the MRI changes associated with SE. In contrast to arterial ischemia, ictal changes on MRI do not follow vascular territories and may affect network structures such as the hippocampus, dentate gyrus, and pulvinar nucleus of the thalamus [84]. In one study of 69 patients with SE, restricted diffusion was seen across cortical or thalamic regions in 19, all of whom had repetitive seizures and LPDs [85]. When MRI changes occur in a region that is generating LPDs, it is possible that the LPDs represent an ictal pattern (Fig. 5.3), but many seizures do not generate restricted diffusion on MRI [48], and in other cases diffusion restriction


(a)
(b)
(c)
(d)
17-18
19-20
21-22
23-24

◀ **Fig. 5.3** Example of lateralized periodic discharges with radiographic ictal correlate. 72-year-old woman with 2 years of progressive Parkinsonism, depression, and hallucinations admitted with psychosis and catatonia. On admission, she developed a secondarily generalized seizure. Continuous EEG monitoring demonstrated: **a** near-continuous waxing and waning 1–1.5 Hz lateralized periodic discharges (LPDs) with superimposed fast and rhythmic frequencies (*black arrowheads*); her mental status was described as obtunded, and she was started on multiple anti-seizure drugs (ASDs) over the course of a 48 h period, during which, **b** the discharges were seen to become higher in voltage and more regular. **c** MRI diffusion weighted sequences demonstrated cortical restricted diffusion in the *left* temporal and parietal lobes and **d** SPECT demonstrated hyperperfusion in the same region. She was intubated and brought to the neurointensive care unit, where continuous infusion midazolam was started. On initiation of midazolam, **e** the previously seen LPDs suddenly became perfectly regular at 1.5 Hz, with a clear maximum at P3. Midazolam was weaned, and over the next few days, **f, g** simply configured stimulus-induced rhythmic, periodic, or ictal discharges were seen at 1 Hz in this same region (stimulation at the vertical red line). These lasted 5–10 s, and no additional ASDs were added. Low titers of voltage-gated potassium channel antibodies were discovered, and she gradually woke up after a course of steroids and rituximab. EEG is displayed in a longitudinal bipolar montage; high frequency filter set at 70 Hz and low frequency filter set at 1 Hz; sensitivity is set at 7 uV/mm

may be confined within the thalamus [86, 87]. Others have noted that MRI changes resolve over days to months, and particularly after SE some T2 signal changes remain persistent [88, 89].

Indirect evidence for the ictal nature of LPDs comes from their emergence from anti-seizure drug (ASD) discontinuation [47, 90] and their prevention or resolution with ASDs [37]. We and others advocate for a *trial of anti-seizure drug therapy* (TOAST) as an important diagnostic step in evaluating patients with LPDs and other periodic or rhythmic patterns [81, 92]. Table 5.3 [91–93] outlines an approach to evaluate LPDs and other periodic or rhythmic patterns when those patterns do not fulfill criteria for nonconvulsive seizures (outlined in previous chapters) when there are no clear ancillary markers of ongoing ictal injury patterns (e.g., MRI, PET, or SPECT changes). We recommend nonsedating ASDs (e.g., levetiracetam) given in doses adequate for treating unequivocal seizures, rather than benzodiazepines where possible, as there are risks for respiratory depression, particularly in the elderly [94]. A TOAST is safe with proper monitoring of cardiopulmonary status.

Lateralized Periodic Discharges: Management

In a survey of 105 neurologists presented with the scenario of LPDs in a lethargic patient the day following termination of NCSE, 15% would add a new ASD, 10% would increase an existing ASD, and 85% would not make any medication changes [95]. Although now 13 years old, this survey highlights persistent equipoise regarding LPDs. Many approaches the management of LPDs by relying on the appearance of the LPDs: for instance, periodic discharges superimposed on a relatively flat background may represent an epileptic encephalopathy as opposed to ongoing ictal activity [96], a reflection of the severity of the underlying brain injury, perhaps warranting less aggressive treatment. On the other hand, periodic discharges with superimposed faster frequencies (LPD+) are highly associated with seizures and may warrant more aggressive treatment [36] (see Fig. 5.3). Although the appearance of LPDs or BIPDs can be informative, the inter-rater agreement for modifier terms and background descriptions is not sufficient to make practice recommendations [5, 97]. Instead, management depends on a proactive diagnostic approach as described above.

When periodic discharges are not clearly ictal and there is no definitive evidence for ongoing neuronal dysfunction, then the management of LPDs depends on the result of a TOAST, described in Table 5.3. If there is clear clinical improvement after an adequate dose of a nonsedating ASD or a benzodiazepine, the ASD should be continued at maintenance dosing and the C-EEG monitored for recurrence of the ictal periodic pattern. If there is evidence suggestive of ongoing neuronal injury and the pattern does not remit with this initial step, additional ASDs may be considered. In a retrospective case-control study, 7/23 (30%) patients with LPDs had clinical and electrographic improvement to ASDs (diazepam or clonazepam, with or without fosphenytoin); interestingly, all seven had LPD+ [74]. Definitive management with "anesthetic" drugs typically used for GCSE, may be warranted in some circumstances.

Often, the background EEG improves despite a lack of clear clinical improvement, and it is not unreasonable to continue maintenance ASD while awaiting a slow improvement in clinical status over the course of 24–48 h [98]. Some consider the restoration of previously absent normal background features (e.g., an alpha frequency posterior dominant rhythm, or sleep transients) an unequivocal trial; but a clinical improvement proximate to the use of ASDs remains the gold standard, defining a pattern as ictal. If a TOAST is inconclusive or negative, the pattern itself may not necessarily require treatment, but rather it may be appropriate to observe the pattern over time while addressing concurrent medical comorbidities. This is particularly true for GPDs, as discussed below.

It should be noted that the use of a TOAST has never been studied for reliability, sensitivity, or specificity. Some ictal discharges, e.g., those associated with refractory SE, may not respond to a single ASD immediately or may

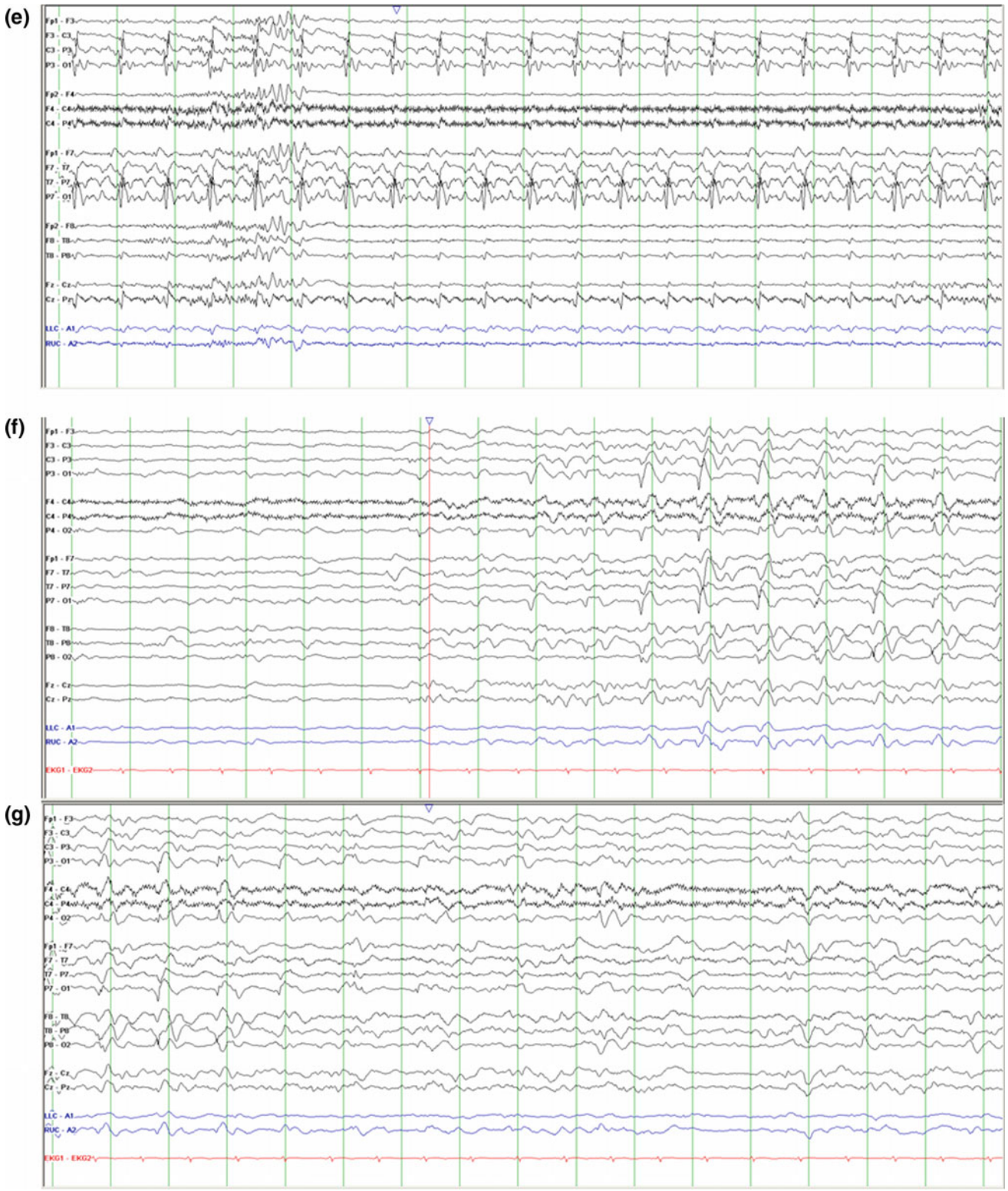


Fig. 5.3 (continued)

Table 5.3 Stepwise approach to performing *a trial of anti-seizure drug therapy* (TOAST) [91–93]

Step	
1	Recognize a periodic or rhythmic pattern that does not fulfill commonly accepted definitions of seizures or status epilepticus and verify that there has been no convincing evidence of ongoing neuronal injury (e.g., new restricted diffusion on MRI in the region of the abnormal pattern; new hyperperfusion on a radiographic flow study)
2	Verify adequate monitoring of blood pressure, cardiac telemetry, and peripheral oxygenation prior to administering medications
3	During continuous video EEG recording *and* in the presence of the periodic or rhythmic discharge, perform a neurologic examination, specifically documenting (on the EEG recording): Level of arousal Any focal neurologic deficits Response of the EEG to stimulation during neurologic exam
4	Administer one of the following, and document (on the EEG recording): Lorazepam 1–2 mg Midazolam 2–5 mg Levetiracetam 30 mg/kg Lacosamide 200 mg
5	After benzodiazepines, monitor for 5–10 min; after ASDs, monitor for 15 min following completion of infusion.
6	Review the EEG and repeat neurologic examination, documenting the same findings as reported previously for comparison
7	If there is no change in the periodic or rhythmic pattern and there is no clinical change, REPEAT step 4–7
8	Interpretation: Positive response: Improvement in the background periodic or rhythmic discharges to <0.5 Hz or <10 second runs **and** Clinical improvement in level of arousal or in focal neurologic deficits, or Restoration of previous absent normal background EEG features, including: Posterior dominant rhythm Sleep transients Inconclusive response: Improvement in the background periodic or rhythmic discharges to <0.5 Hz or <10 second runs **and** No clear clinical improvement, or Decrease in the level of arousal No response: No improvement in the background periodic or rhythmic discharges **and** Decrease in level of arousal, or Signs of respiratory depression or cardiovascular instability (e.g., hypotension or cardiac arrhythmia)

require more aggressive therapy in order to achieve seizure freedom. Conversely, ASDs can attenuate waveforms that are potentially non-ictal, such as some GPDs with Triphasic Morphology [99], discussed later in this chapter. Finally, decreasing the discharge frequency of, or complete resolution of, LPDs may reflect the natural history of the discharges rather than a specific response to an ASD, depending on the acuity of the underlying etiology.

We recommend ASD prophylaxis routinely when LPDs are seen during C-EEG recording because of their close association with seizures. Although the choice of ASD is often debated, an ideal agent should cover both focal and generalized seizures, with minimal medication interactions and relatively rapid titration. Phenytoin has been used as prophylaxis for acute seizures after acquired brain injury [100], but others have shown similar efficacy for seizure prevention using levetiracetam [101], which exhibits far fewer side effects. Valproic acid and lacosamide are used in some cases, depending on the patient.

In a series of 24 patients with LPDs, 11 of 15 adults with LPDs developed later epilepsy [49]. In a case-control series, 48.1% of patients with LPDs developed epilepsy compared with 15.7% of controls [74], but in multivariate analysis this was not an independent association. Whereas some have proposed treating patients with LPDs long-term based on these risks [46, 78], others taper ASDs during hospitalization provided no unequivocal seizures are recorded. The majority of patients with LPDs have an acute symptomatic cause, and the prevention of acute seizures after acquired brain injury has not shown a decrease in the incidence of subsequent epilepsy. Therefore, we reason that only a short course (7 days or through the hospitalization) of ASDs is warranted to prevent seizures during the acute illness. On the other hand, those who exhibit clinical seizures or develop unequivocal

electrographic seizures may be at increased risk for epilepsy and may warrant a longer term treatment. We recommend a 3–6 month course of ASDs, with consultation with a neurologist or epileptologist prior to weaning medication.

Bilateral Independent Periodic Discharges

BIPDs have been described since the earliest mention of LPDs [22], but there have been few studies of BIPDs, in part because they are less commonly recorded. BIPDs have been reported in approximately 0.1% of patients undergoing routine or outpatient EEG, and in 1–5% of C-EEG [34, 46, 102]. Table 5.4 lists the etiologies associated with BIPDs. Whereas LPDs have a stronger association with focal seizures (albeit coexisting at times with BIPDs), BIPDs have a greater association with generalized seizures [102]. BIPD+ patterns are invariably associated with seizures [46]. Clinically, BIPDs are less often associated with focal neurologic deficits and more with coma, likely as a result of bilateral cortical involvement. While BIPDs have traditionally been associated with substantial mortality (52–61% according to most series [46, 102]), thus far there have been no dedicated case-control series to confirm an independent association. The substantial mortality seen in patients with BIPDs likely reflects the severity of the underlying etiology, but more than 20% of patients with BIPDs in one series were living independently at a mean follow up of 18 months [34], and relatively benign BIPDs have been documented after bilateral strokes [103]. When controlling for disease severity after SAH or ICH, BIPDs have not been found to confer an independent risk for poor outcome, in contrast to LPDs [68, 69].

Generalized Periodic Discharges (GPDs)

GPDs are described as synchronous, bihemispheric periodic discharges [30]. GPDs may co-occur with LPDs (21.5%, vs. 10% of controls matched for age, etiology, and level of arousal) and BIPDs (10.5% vs. 1.5%) [30]. Clinically, GPDs are associated with lethargy or coma in 92% of cases. Myoclonus is sometimes seen in conjunction with specific disease processes associated with GPDs, such as Creutzfeldt–Jakob disease (CJD) or anoxic ischemic injury. Other causes of GPDs are listed in Table 5.5 [30, 34, 44, 60, 104–112]. GPDs have been variably subclassified. ("triphasic morphology," the most common subtype of GPDs, will be discussed separately.) Prior reviews have distinguished periodic short-interval diffuse discharges (PSIDDs), which occurs every 0.5–4 s, from periodic long-interval diffuse discharges (PLIDDs), which are polyphasic and occur every 4–30 s [113]. The standardized ACNS terminology regards polyphasic discharges as bursts with >4 phases, and PLIDDs would now be classified as either a burst–suppression pattern or, when background activity is preserved, continuous with high-amplitude bursts [4]. PLIDDs have a close association with subacute sclerosing panencephalitis (SSPE), a now rare form of progressive degenerative post-measles encephalitis, and have been observed with ketamine or PCP toxicity. While anoxia is clearly associated with burst–suppression on EEG, "burst–suppression with identical bursts" is a regular, recurrent polyphasic bursting pattern seen after severe diffuse anoxia and may be considered part of the PLIDD category. A retrospective blinded study of 101 cardiac arrest patients following return of spontaneous circulation found this pattern in 20, all of whom had poor six month neurologic outcome (CPC 3–6), compared with 10 of 28 patients with poor outcome and a more typical suppression–burst pattern [114]. This chapter will focus on short-interval GPDs.

The pathophysiology underlying the periodicity exhibited by GPDs likely overlaps with that of periodic discharges in general, described above. Computational modeling suggests that selective loss of glutamatergic signaling at cortical interneurons results in a diffuse and periodic pattern similar to GPDs [115]. Animal studies have demonstrated that interneuronal excitatory glutamatergic synapses are far more

Table 5.4 Etiologies of bilateral independent periodic discharges [46, 102]

Category	Etiology
Neurovascular	Anoxic encephalopathy Bihemispheric infarcts Cerebral vasculitis Sickle cell disease Amyloid angiopathy
Infection, inflammation, neurodegeneration, autoimmune	Herpes simplex virus encephalitis Bacterial meningitis (haemophilus influenza, *Klebsiella pneumoniae*) Other viral encephalitis (adenoviral encephalitis) Hashimoto encephalopathy
Systemic illness	Hepatic encephalopathy Alcohol-related seizures
Degenerative	Creuzfeldt–Jacob Disease

Table 5.5 Etiologies of generalized periodic discharges (GPDs) [30, 34, 44, 60, 104–112]

Category	Etiology of GPDs	Etiology of GPDs with triphasic morphology
Neurovascular	Hypoxic encephalopathy Acute ischemic stroke Subarachnoid hemorrhage Intraventricular hemorrhage Intracerebral hemorrhage	Anoxic encephalopathy Pontine ischemic stroke Binswanger encephalopathy Cerebellar hematoma
Space occupying lesion, malignancy	Acute hydrocephalus Central nervous system tumor	Hydrocephalus Midline diencephalic structures (glioma, craniopharyngioma) Cerebral carcinomatosis Multifocal cerebral lymphoma
Infection, inflammation, autoimmune	Sepsis Herpes encephalitis Subacute sclerosing panencephalitis	Sepsis Herpes encephalitis Neuroborreliosis NMDAR encephalitis VGKC encephalitis Steroid-responsive encephalopathy with anti-thyroid antibodies, or Hashimoto encephalopathy
Trauma	Subdural hematoma Traumatic brain injury	
Systemic Illness	Hepatic encephalopathy Uremia or renal failure Hyponatremia Hypoglycemia Hypothyroidism	Hepatic insufficiency/hyperammonemia Uremia or renal Failure Hypernatremia/hyponatremia Hypoglycemia Hyperthyroidism/hypothyroidism/thyroiditis Hypercalcemia Hypoxia/hyperventilation Hyperosmolarity (e.g., hyperglycemia) Addison disease
Epilepsy	Epileptic encephalopathy Postictal state Lennox–Gastaut	
Neurodegenerative	Creutzfeldt–Jakob disease Alzheimer disease Gaucher disease	Creutzfeldt–Jakob disease Alzheimer disease Bilateral basal ganglia calcification
Toxicity	Withdrawal from barbiturates, benzodiazepines, or propofol Phencyclidine (PCP) or ketamine Lithium Baclofen L-Dopa Ifosfamide Cefepime and other cephalosporins Dialysis-associated encephalopathy	Naproxen Baclofen Lithium Metrizamide Cefepime and other cephalosporins

NMDAR N-methyl-D-aspartate receptor
VGCK voltage-gated potassium channel

prone to ischemic injury than are the inhibitory GABAergic neurons after an anoxic injury [116]. Animal and neuronal cell culture studies further demonstrate that anoxic postsynaptic cortical neurons continue to generate their own action potentials, either spontaneously or in response to applied glutamate but not presynaptic stimulation [117, 118]. Histologic studies in patients with degenerative brain disease have demonstrated networks of damaged cortical and subcortical gray matter [7], which may similarly alter the balance between cortical inhibition and excitation. Still, the distribution of GPDs suggests at the very least that diffuse cortical synchrony is mediated by intact thalamocortical networks. *Epileptic seizure* discharges propagating via these same thalamocortical networks may manifest as GPDs, whether from a focal or a distributed source, e.g., one case report describes stimulation of the centromedian thalamic

nucleus bilaterally with immediate resolution of ictal GPDs [119].

GPDs have a prevalence of 0.06% in routine EEG recordings [34] and 4.5–5.5% among hospitalized patients requiring C-EEG [30]. GPDs are highly associated with electrographic seizures and SE, with one study reporting nonconvulsive seizures in 26.5% of patients with GPDs, compared with just 7.5% in age, etiology, and mental status matched controls. This association held true whether GPDs co-occurred with LPDs/BIPDs or not [30]. Although the majority of seizures in patients with GPDs were generalized, 46.4% were focal. Predicting which patterns are more highly associated with seizures is challenging clinically. In a study of 25 patients with GPDs (excluding burst suppression or continuous GPDs with Triphasic Morphology), those in SE had statistically significantly greater discharge and inter-discharge amplitudes (110 vs. 80 μV, and 34 vs. 17 μV) and longer duration (0.5 vs. 0.3 s) [104]. Similar to the case with other periodic discharges, the presence of superimposed faster frequencies and sharpness independently increase the odds that GPDs will be associated with seizures [97].

GPDs correlate with a 41–64% in hospital mortality (even when excluding invariably fatal neurodegenerative processes such as CJD or SSPE [30, 74, 104, 105], but their presence is not an independent risk factor for outcome when compared to age, etiology, and mental status matched controls [30]. Others have found that after SE, SAH, or ICH, GPDs do not appear to confer an independent risk for poor outcome [68, 69, 72]. Both short and long-term recovery to independence are seen in nearly one in five patients with GPDs [30, 34]. When survivors of cardiac arrest are excluded, the presence of GPDs may be associated with inhospital death, but this has not been confirmed [30]. One study found that patients with GPDs who were alive at discharge were significantly more likely to be younger (mean age 51 vs. 68 years) and have better mental status at the time of EEG placement and higher inter-GPD amplitudes (33 vs. 18 μV) [104]. The presence of superimposed fast frequencies (GPD+) and the absence of background reactivity appear to increase the odds for poor outcome independently [21, 97], although this should be confirmed before being used for clinical decision making.

Generalized Periodic Discharges with Triphasic Morphology

Previously termed "triphasic waves," GPDs with Triphasic Morphology are a subtype of GPDs described originally in the context of hepatic encephalopathy [120]. "Triphasic" refers to an initial negative phase followed by a positive, dominant phase, usually followed by a third negative phase. GPDs with Triphasic Morphology appear as "blunt spike-and-wave" complexes and classically exhibit phase lag, a temporal dispersion across the scalp EEG, and modulate with state or stimulation. GPDs with Triphasic Morphology have been attributed to thalamocortical dysfunction because of the accompanying development of frontal release signs, upper motor neuron findings, and pathologic changes to the lenticular and dentate nuclei during hepatic encephalopathy [120]. Although traditionally associated with metabolic encephalopathies, GPDs with Triphasic Morphology have been described in a wide variety of illnesses (see Table 5.5).

The standardized ACNS terminology [4] uses the term "Triphasic Morphology" as a modification of the more general term GPDs. While the terms "generalized" and "periodic" exhibit almost perfect agreement, with an inter-rater agreement (IRA) with $\kappa = 0.81$, a blinded study of EEGs reviewed by multiple critical care EEG experts found poor IRA for "Triphasic Morphology" ($\kappa = 0.33$), despite the finding that these experts were more likely to call a specific GPD pattern "triphasic" when it exhibited typical findings such as a dominant second or third phase, or a phase lag [97]. In a case-control series of patients with encephalopathy matched for mental status, those with GPDs with Triphasic Morphology were more likely to have liver insufficiency, respiratory tract infection, or a history of alcohol abuse [21], although patients with seizures were specifically excluded from this cohort. EEGs interpreted by blinded reviewers as having GPDs with a Triphasic Morphology were actually less likely to come from a patient with a toxic-metabolic encephalopathy [97]. In general, the descriptor "triphasic waves" is not a reliable indicator of the presence of toxic-metabolic encephalopathy in the absence of further clinical information.

The corollary is that distinguishing between GPDs that might be associated with seizures and those due to an underlying toxic-metabolic encephalopathy (and therefore not likely to be associated with seizures) is difficult in clinical practice. In some cases, GPDs with triphasic morphology have been described as a clearly ictal pattern [106, 121, 122]. Clinically, the gradual onset of an encephalopathy with signs such as asterixis suggests an underlying toxic-metabolic cause, in contrast to a sudden decline in mental status with focal neurologic findings [123], but GPDs are bihemispheric and may only manifest as coma with or without some of the nonspecific findings associated with nonconvulsive seizures, including asterixis [3]. *Post hoc*, GPDs *not* associated with seizures exhibit a lower frequency (1.8 vs. 2.4 Hz), longer phase one, phase two lag, fewer extra-spike components, greater generalized background slowing, and stimulation-dependence [124, 125]. EEGs

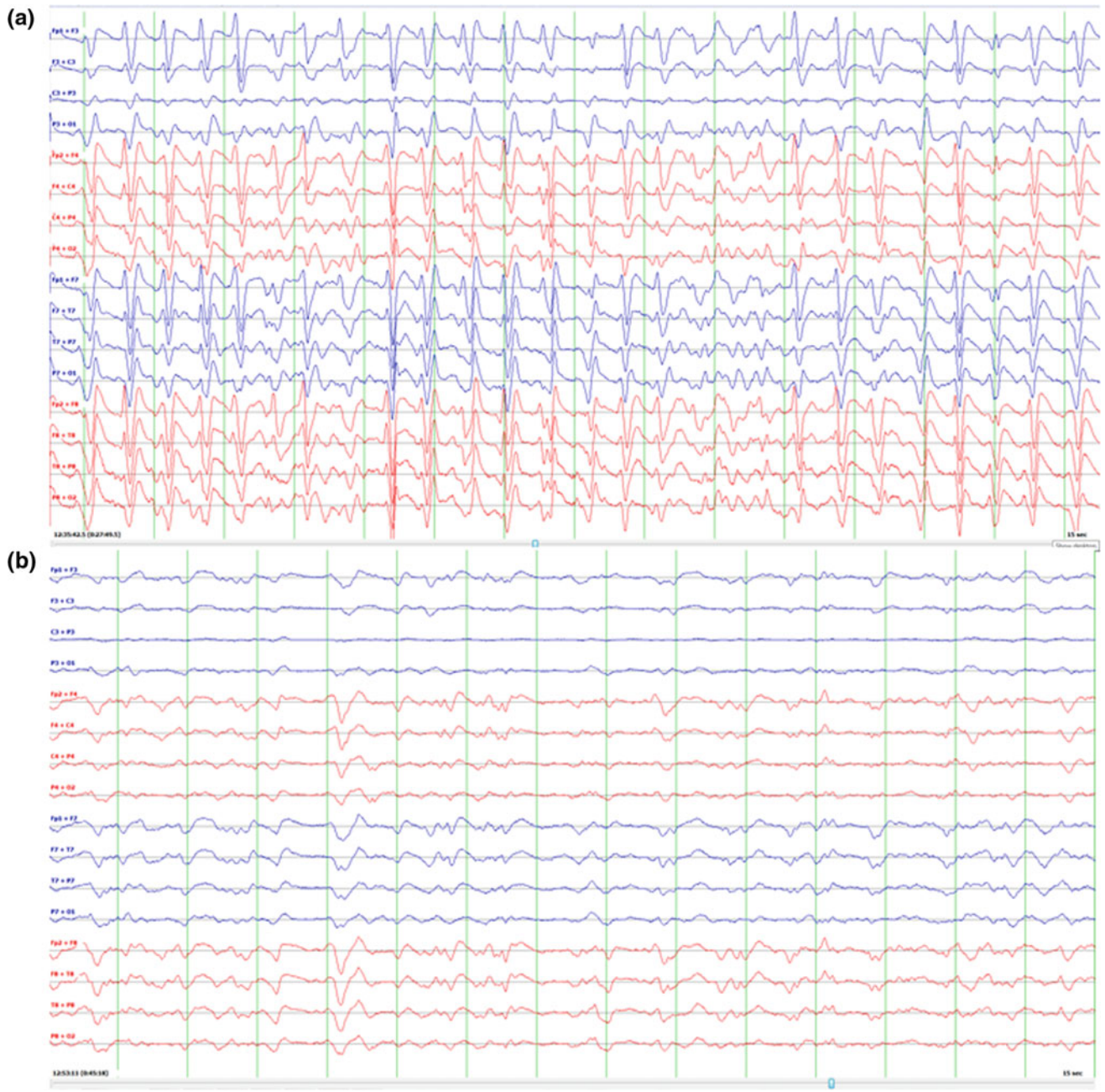


Fig. 5.4 Generalized periodic discharges with inconclusive trial of anti-seizure drug therapy. 62-year-old man with end-stage renal disease admitted with sepsis requiring continuous venovenous hemodialysis and broad-spectrum antibiotics including cefepime were begun. Sedation was withheld, but he did not wake up. **a** Abundant state-dependent, 2 Hz generalized periodic discharges with Triphasic Morphology were seen superimposed on a moderately slow and poorly organized background. **b** After a total of 4 mg midazolam, no clear clinical changes were observed but the EEG demonstrated a much less regular, slower discharge frequency. This is considered an inconclusive trial of anti-seizure drug therapy. Levetiracetam was started at renal dosing, and cefepime was stopped. During the next several days, the patient's mental status improved gradually with continued dialysis, suggesting a cefepime-induced encephalopathy. EEG is displayed in a longitudinal bipolar montage; low frequency filter set at 1 Hz and high frequency filter set at 70 Hz; sensitivity is set at 7 uV/mm

judged to have GPDs with Triphasic Morphology, however, are just as likely to come from patients with unequivocal seizures (25%) as from those without a Triphasic Morphology (26%) [97]. Making a distinction between subtypes of GPDs based solely on EEG is not recommended without obtaining further clinical information.

Generalized Periodic Discharges: Diagnostic Approach and Management

When GPDs are encountered, the initial diagnostic priority is establishing whether or not they represent an ictal pattern. If the GPDs do not meet standard definitions of nonconvulsive seizures or SE based on their electrographic features (such as a discharge frequency of >2.5 Hz or clear evolution in frequency, morphology, or location), their relationship with clinical symptoms should be established. For instance, after cardiac arrest, myoclonic activity may occur in conjunction with GPDs. When these are time-locked, GPDs should be considered ictal; but when myoclonus is present in this setting, its timing is often distinct from that of the GPDs. Other clinical and radiographic ictal correlates (coma, cortical regions of restricted diffusion on MRI) are confounded after cardiac arrest by the ischemic injury. Some have proposed that treatment of GPDs following cardiac arrest is probably futile based on the underlying pathophysiology [115], and in one study of 47 patients with electrographic SE, including continuous GPDs >0.5 Hz, those with good outcome were less often treated with ASDs—not more often. This may have reflected a bias of the clinical interpretation of the EEG or merely the futility of treating GPDs that follow cardiac arrest when they occur over a discontinuous background or fail to remit [18]. This specific clinical scenario is being activity investigated in the context of a multicenter clinical trial [126].

In some cases, a clear cause or precipitant of GPDs (e.g., fulminant hepatic failure, or the initiation of cefepime in a patient with renal failure) may be identified and where possible, corrected. Because GPDs have a clear association with seizures; however, we recommend a TOAST in the majority of cases and at least a short (7 day) course of an ASD while the acute illness is being addressed (Fig. 5.4). In the only study evaluating responses to a TOAST, 64 patients with GPDs with Triphasic Morphology were evaluated. Ten of 53 (19%) had a clear positive response to benzodiazepines (always immediately), while 19/45 (42%) had a positive response to nonsedating ASDs, the majority of which were delayed >2 h [93].

Generalized Periodic Discharges: Relationship with Creutzfeldt–Jakob Disease

GPDs have been associated with prion disease for nearly as long as they have been described [127]. GPDs are seen in 60–70% of sporadic and iatrogenic CJD and in 10% or less of genetic CJD (e.g., fatal familial insomnia or Gerstmann–Sträussler–Scheinker syndrome) [128, 129]. GPDs have not been described in variant, or bovine spongiform encephalopathy-related, CJD [129]. Periodic sharp waves at approximately 1 Hz appear around 12 weeks after symptom onset [130], with maximum activity around the 15th week post symptom-onset [131] but can manifest as early as the second week [132]. Activity is often maximal in the frontal regions but can be confined to the occipital cortex, for instance in the Heidenhain variant of CJD [133]. Early recordings may demonstrate prominent asymmetry, even resembling LPDs [134], but gradually, these become symmetric. GPDs in prion disease often exhibit a Triphasic Morphology [135], and they seem to resolve with sleep and attenuate with stimulation (unlike most LPDs) and sedating medications. In iatrogenic CJD, the discharges are more localized to the site of inoculation [129]. Seizures are uncommon, occurring in <15% even in those with the highest incidence of GPDs [129]. Myoclonus is observed frequently, but the myoclonic jerks are not time-locked to the GPDs [132].

GPDs are 64–66% sensitive and 74–91% specific for CJD when presenting in the context of a typical clinical syndrome [135, 136] and are part of the World Health Organizations diagnostic criteria for the clinical diagnosis of CJD. GPDs, however, are also found with other rapidly progressive dementias. There are case reports of voltage-gated potassium channel antibody encephalitis [137, 138] and steroid-responsive encephalopathy with anti-thyroid antibodies (formerly known as Hashimoto Encephalopathy) [139] mimicking CJD, and it is not unreasonable to approach these periodic discharges as any others: a clue, but not a definitive sign, of a differential that includes treatable and untreatable etiologies.

Rhythmic Delta Activity

Rhythmic delta activity (RDA) may be lateralized (LRDA) or generalized (GRDA), referred to commonly as frontally predominant, intermittent rhythmic delta activity (FIRDA). Lateralized rhythmic patterns include those described originally in patients with epilepsy. Temporal intermittent rhythmic delta (TIRDA) has been described in conjunction with ipsilateral mesial temporal lobe epilepsy and is an epileptiform equivalent. Occipital intermittent rhythmic delta, although not specific for epilepsy, is closely associated with primary generalized epilepsies and is more common in children and younger adults [140, 141]. More recently, LRDA has been explored as a pattern seen in the context of critical care EEG monitoring. In a study of 558 patients undergoing C-EEG, the incidence of LRDA was 4.7% and seen primarily in patients with acute or remote brain injuries [40]. Like LPDs, the majority have focal neurologic signs, and LPDs co-occur in patients with LRDA more frequently than in patients with focal slowing. As opposed to LPDs, LRDA and other forms of rhythmic delta

activity occur intermittently in runs lasting less than a minute rather than in a sustained periodic pattern. LRDA is highly associated with acute seizures, which were reported in 63% of those with LRDA, nearly all of which were nonconvulsive [40].

GRDA is described as bilateral, synchronous rhythmic discharges, usually with a frontal predominance. Frontally, predominant GRDA has been found in 0.1–1% of routine EEGs [142, 143] and in 6–17% of EEGs in hospital-based series [29, 141]. GRDA is less specific than LRDA; Table 5.6 [140–148] lists etiologies described in the literature. Frontally predominant GRDA was originally thought to be specific for deep midline or posterior fossa lesions, and in fact is seen in 11–17% of posterior fossa pathologies [142, 144]. Supratentorial and lateralized structural lesions, however, increased the odds for the development of frontally predominant GRDA nearly fivefold in one case-control study [141]. If the EEG background is abnormal, frontally predominant GRDA may be a transient finding in the setting of metabolic encephalopathy [143]. Clinically, 75% of patients with frontally predominant GRDA had a normal level of arousal and one-third had a normal neurologic exam [143], although encephalopathy is more common in those with frontally predominant GRDA, occurring in 63% [141]. Coma is a *less* common clinical manifestation of GRDA, in contrast to BIPDs or GPDs.

Seizures have been found only rarely in association with GRDA, and compared with controls, epileptiform discharges are also much less common [141]. GRDA has been reported *after* seizures but is not thought to represent an ongoing ictal pattern after seizures [145] with the exception of limbic SE, which may present as longer runs of higher amplitude RDA [149]. Multifocal structural abnormalities could theoretically create a GRDA pattern, much in the way a focal lesion creates LRDA. Similarly, deep seizure foci propagating via the dorsomedial thalamus [142], which connects limbic and pre-frontal networks, may manifest as GRDA. For both LRDA and GRDA, a pattern duration of >10 s in the setting of decreased level of arousal should prompt further investigation, including a TOAST, in order to determine if the rhythmic discharges are ictal (Fig. 5.5). We do not recommend ASDs as a prophylactic measure in patients with GRDA, but this may be reasonable in patients who develop LRDA in the context of an acute brain injury.

Table 5.6 Etiologies of rhythmic delta activity [140–148]

Category	Etiology
Neurovascular	Ischemic stroke Intracerebral hemorrhage (deep) Subarachnoid hemorrhage Arterio-venous malformations Anoxic Venous thrombosis Carotid occlusion Hyperventilation
Space occupying lesion, malignancy	Posterior fossa/third ventricular tumors Aqueductal stenosis and hydrocephalus Cortical-based tumors Increased intracranial pressure
Infection, inflammation, autoimmune	Cerebral edema Abscess Encephalitis Progressive multifocal leukoencephalopathy Posterior reversible encephalopathy syndrome Systemic lupus erythematosus
Trauma	Subdural hematoma Traumatic brain injury Medial frontal lobotomy
Systemic Illness	Metabolic encephalopathy Renal failure
Epilepsy	Epilepsy, focal and symptomatic generalized Post ictal
Migraine	Basilar artery migraine
Neurodegenerative	Lewy body disease Progressive supranuclear palsy Corticobasal degeneration Creutzfeldt–Jakob disease

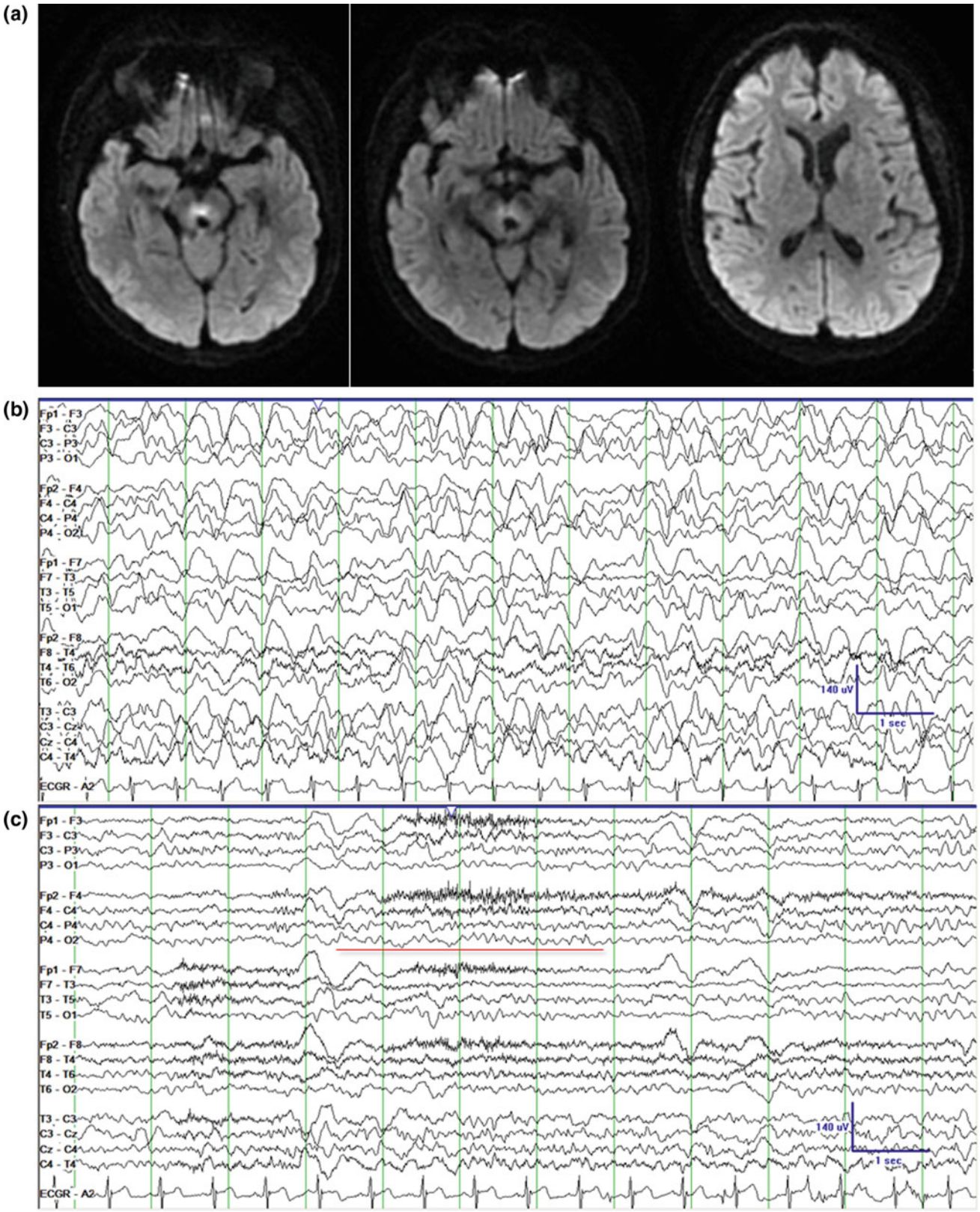

(a)
(b)
Fp1 - F3
F3 - C3
C3 - P3
P3 - O1
Fp2 - F4
F4 - C4
C4 - P4
P4 - O2
Fp1 - F7
F7 - T3
T3 - T5
T5 - O1
Fp2 - F8
F8 - T4
T4 - T6
T6 - O2
T3 - C3
C3 - Cz
Cz - C4
C4 - T4
ECGR - A2
140 uV
1 sec
(c)
Fp1 - F3
F3 - C3
C3 - P3
P3 - O1
Fp2 - F4
F4 - C4
C4 - P4
P4 - O2
Fp1 - F7
F7 - T3
T3 - T5
T5 - O1
Fp2 - F8
F8 - T4
T4 - T6
T6 - O2
T3 - C3
C3 - Cz
Cz - C4
C4 - T4
ECGR - A2
140 uV
1 sec

Fig. 5.5 Generalized rhythmic delta activity with a trial of anti-seizure drug therapy. 54-year-old woman with a 4th ventricular hemorrhage and extension of clot into the aqueduct. After external ventricular drainage and suboccipital clot evacuation, she gradually began following commands. One week post-operatively, she followed commands less clearly and developed coarse, irregular asterixis. **a** MRI diffuse-weighted sequence demonstrates a region of peri-hematomal infarct centered in the midbrain, along with residual aqueductal clot (*dark*) but no supratentorial infarct and no hydrocephalus. **b** The initial recording demonstrated intermediate duration high-amplitude frontally predominant generalized rhythmic delta activity waxing and waning up to 2.5 Hz, at times with embedded sharply contoured waveforms. **c** 2 mg lorazepam was administered, at which point the patient followed commands more briskly, and the background EEG demonstrated a posterior dominant rhythm (*underlined in red on the right side*) at 7.5 Hz, consistent with mild diffuse background slowing. Levetiracetam was started, and the rhythmic delta activity abated over the next several days. This is considered a positive provocative anti-seizure drug trial, and these discharges were considered to be potentially ictal. EEG is displayed in a longitudinal bipolar montage; low frequency filter set at 1 Hz and high frequency filter set at 70 Hz; sensitivity is set at 7 uV/mm

Stimulus-Induced Rhythmic, Periodic, or Ictal Discharges

Stimulus-induced rhythmic, periodic, or ictal discharges (SIRPIDs) are abnormal rhythmic or periodic patterns that occur consistently as a result of alerting stimulation [150]. The stimulation required to generate SIRPIDs may be subtle (e.g., a ventilator alarm or a voice outside the hospital room), but noxious stimulation is usually required, such as endotracheal catheter suctioning, and the phenomenon is become increasing recognized as video C-EEG monitoring has become standard in many critical care units. SIRPIDs have been described in 10–22% of patients undergoing C-EEG [151] and have been associated with a variety of critical brain injuries including SAH, ICH, ischemic stroke, hyponatremia, TBI, and particularly, post-anoxic encephalopathy—which is independently associated with SIRPIDs [151, 152]. Clinically, patients with SIRPIDs are comatose and SIRPIDs occur in a delayed fashion after the initial injury or insult. After cardiac arrest, for instance, SIRPIDs appear after a mean of 139 h [152], and in the neurointensive care unit, prolonged periodic discharges (lasting longer than 5 days) increase the risk for SIRPIDs [39]. In a study of 43 patients with SIRPIDs from a cohort of 416 patients undergoing C-EEG monitoring, stimulus-induced patterns lasted a mean of 60 s [151]. SIRPIDs are periodic in 60% of cases and rhythmic in 40% [150, 151]. SIRPIDs do not have an independent association with mortality once age and etiology (specifically, anoxia) are accounted for [151].

SIRPIDS are associated with inhospital seizures [39, 151, 153]—reported in 28–52% of those with SIRPIDs [150, 151]. They are considered ictal in 10–50% of cases [150, 151] based on the appearance of evolution in frequency, location, or morphology. There is some debate about the nature of ictal-appearing SIRPIDs: two studies have demonstrated a lack of hyperperfusion in two patients with SIRPIDs during an "ictal" SPECT compared with an interictal SPECT, but three other patients had significant confounders [154, 155]. All three had had recent unequivocal nonconvulsive SE, and one had chronic ipsilateral carotid disease with decreased time to peak on vascular imaging, which likely interfered with interpretation of the flow study. Because of the association between SIRPIDs and electrographic seizures, we consider ASD prophylaxis in patients with periodic or ictal-appearing SIRPIDs. Stimulus-induced frontally predominant GRDA is typically monitored without ASD prophylaxis unless there is compelling additional clinical information. In the setting of acute brain injury, it is not unreasonable to limit stimulation when SIRPIDs occur until more definitive information regarding their potential impact on brain injury and outcome becomes available.

Conclusion

Periodic and rhythmic patterns are encountered with increasing frequency as continuous EEG monitoring is adopted more widely across hospitals and intensive care units for seizure detection and brain monitoring. A standardized nomenclature has provided a common way to describe these abnormal patterns. In most cases, periodic and rhythmic discharges do not indicate a specific underlying diagnosis, but instead represent a common expression of a variety of underlying pathologies. LPDs in particular may independently affect outcome, and there is mounting evidence that periodic discharges exacerbate underlying acute brain injury. LPDs, GPDs, LRDA and SIRPIDs are highly associated with electrographic seizures during C-EEG monitoring, and it is critical to consider any periodic or rhythmic pattern as potentially ictal if there is a clinical correlate, evidence of ongoing neuronal injury, or a positive response to an ASD.

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Imaging in Status Epilepticus

6

Jonathan C. Edwards, Diana M. Gomez-Hassan, and Leonardo Bonilha

Practical Considerations for Imaging in Status Epilepticus

Imaging during generalized convulsive status epilepticus (GCSE) is difficult or impossible, so most reported images come from patients postictally after GCSE or with imaging during nonconvulsive SE (NCSE). In many cases, at the time of diagnosis of SE, the only imaging already obtained is a screening computed tomography (CT) scan. Once the diagnosis of SE has been established (on clinical grounds for GCSE, or clinically or by electroencephalography (EEG) or both for NCSE), the focus turns to the termination of seizures as quickly as possible. Further imaging with other modalities usually must wait until the patient is stable and the SE has been controlled successfully. Patients undergoing treatment for SE may have hemodynamic instability and require mechanical ventilation, necessitating close monitoring and creating further challenges in obtaining detailed or multimodal imaging.

The literature on neuroimaging during SE is limited, and large controlled series are not available. Nonetheless, modern imaging facilities include protocols for CT, magnetic resonance imaging (MRI), positron emission tomography (PET), and single-photon emission computerized tomography (SPECT) in critically ill patients.

J.C. Edwards (✉) · L. Bonilha
Department of Neurology, Clinical Neurophysiology Laboratories, Clinical Services, MUSC Comprehensive Epilepsy Center, The Medical University of South Carolina, Clinical Science Building Suite 30796, Jonathan Lucas St, Charleston, SC 29425-6160, USA
e-mail: edwardjc@musc.edu

L. Bonilha
e-mail: bonilha@musc.edu

D.M. Gomez-Hassan
Department of Radiology, University of Michigan Hospitals, 1500 East Medical Center Dr, Ann Arbor, MI 48109, USA
e-mail: dmgh@umich.edu

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Most intensive care patients with external monitors, lines, and devices including ventilatory equipment can undergo CT or SPECT studies safely. Certain pieces of medical equipment on or near the patient's head may result in streak artifacts on CT images or defects on SPECT images, requiring patient repositioning to avoid these artifacts. If contrast-enhanced imaging is needed, patients must be evaluated for potential reactions to intravenous contrast material. Although uncommon, a severe reaction to contrast material can be life-threatening, and these studies must be performed when physicians are present to manage any possible adverse reactions.

For MRI, trained personnel are needed to verify that the patient can undergo the study safely. Patients with invasive blood pressure measuring devices, pacemaker wires, and infusion pumps may not undergo MRI studies. Metallic implants, devices, stimulators are contraindications to MRI imaging unless specified as MRI-compatible. For critical care patients, nonferromagnetic supportive equipment, including ventilators, IV lines, tubes, and monitors must be verified for MRI-compatibility. In addition to the MRI technologist, adequately trained critical care and anesthesia personnel are required; although time-consuming, their presence is critical for patient safety. While most university or tertiary care centers have trained staff and MRI-compatible equipment and accessories, some centers may not be able to perform MRI on critical care patients, precluding its widespread use in SE.

Computed Tomography

CT is an important diagnostic tool in the screening for intracranial lesions such as hemorrhage or mass, especially in the acute setting, but it is suboptimal for evaluating details of brain parenchyma. Patients presenting in SE can be screened easily with a noncontrast or contrast-enhanced head CT, but the yield of these studies is low, particularly in patients with long-standing epilepsy.

The main advantages of CT are its availability in most institutions and the short time needed for scanning. State-of-the-art 64-slice helical CT scanners can perform a head CT in less than 10 s, but additional time is needed to position the patient and obtain the appropriate scout images prior to the CT. The entire process can require 10–15 min. Contrast-enhanced CT imaging generally adds 10–15 min for administering the contrast and incorporating a delay for proper enhancement. Another advantage is that osseous structures, surgical clips, and cerebral hemorrhages are seen better on CT than on MRI. Indeed, epilepsy patients with intracranial and extracranial electrodes are often imaged with CT to assess the position of the leads. Finally, CT scan of the head is less expensive than MRI.

CT requires the use of radiation, although this disadvantage is minimized by the use of multislice high-speed scanners optimized to reduce radiation exposure. The greatest disadvantage of CT is its low sensitivity compared to MRI in detecting parenchymal brain abnormalities in patients with seizures and epilepsy.

Overall, the sensitivity for detecting any CT abnormality in a patient with epilepsy ranges from 30 to 40%. Although not systematically evaluated to date, the sensitivity and specificity of CT scans in SE are likely to be significantly lower. CT may have a role in identifying acute or large structural abnormalities in patients presenting in SE, but it has a limited diagnostic role in evaluating more subtle cortical malformations or parenchymal signal abnormalities.

CT findings reported in patients with NCSE are often nonspecific. Transient changes during the acute stage of SE have been detected. Bauer and colleagues reported a patient in SE for 2 days with focal right frontal cortical swelling (with narrow sulci and a hypodensity in the right frontal lobe) subsequently confirmed by MRI; these changes resolved after cessation of the seizures [1]. In another case from our center, however, a CT scan on a patient with a known left frontal abscess (previously treated medically and surgically) showed no new changes when the patient presented in NCSE. The subtle parenchymal distortion in the left frontal region due to the earlier abscess was seen again (Fig. 6.1), but no additional changes related to the NCSE were evident.

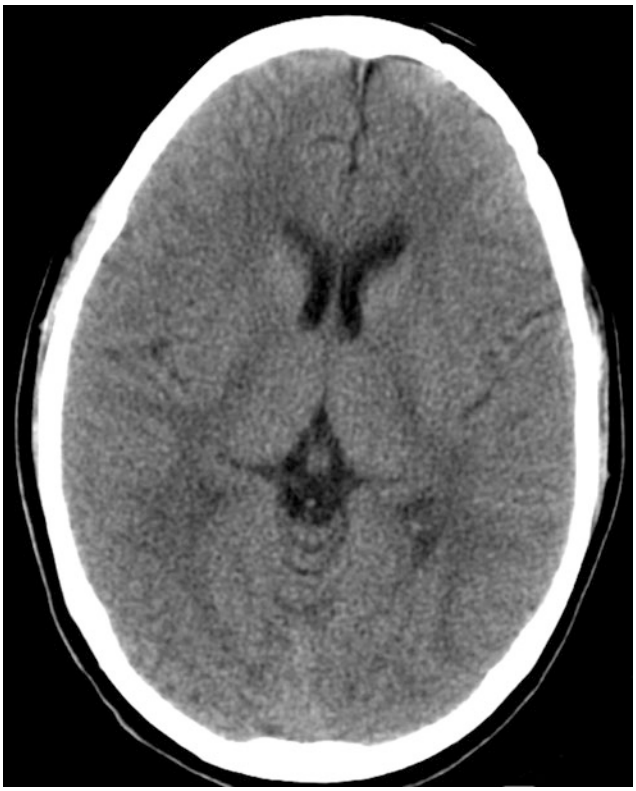

Fig. 6.1 Computed tomography (*CT*) scan of a 16-year-old girl with an earlier history of pansinusitis and a left frontal cerebritis and abscess who had undergone surgical treatment and presents 4 months later with nonconvulsive status epilepticus

Magnetic Resonance Imaging

MRI is an essential tool for the evaluation of patients with epilepsy, but may have a more limited application in SE. MRI technology, including equipment, field strength, and software are being optimized continuously for better resolution, and MRI provides far greater resolution of brain structures compared to that of other imaging. Rather than radiation, MRI uses radiofrequency pulses and magnetic fields to change atomic spins temporarily and generate images. Although the lack of ionizing radiation is an advantage, magnetic fields can be dangerous in patients with internal pacemaker wires, stimulators, or other ferromagnetic implants. MRI has become widely available, but high field strength scanners and several particular scanning sequences and acquisition protocols may be available at multidisciplinary epilepsy centers only.

Among potential limitations of MRI, a routine study of the brain may take from 30 to 60 min, and a high-resolution epilepsy-focused MRI, 60–90 min. Immobility of the patient is essential for maximal image resolution; even subtle movement, including swallowing or eye blinking, can compromise the image quality. Usually, multiple sequences must be obtained, requiring greater cooperation by the patient to remain still. For these reasons, patients in NCSE may have an initial screening MRI to assess for acute changes, followed by a separate study to improve resolution of the imaging. The sequences used in epilepsy-focused protocols can take as long as 9–11 min each—compared to 2–4 min each for screening studies. MRI-compatible surgical clips, coils, shunts, and other hardware can also distort the images. Patients needing ventilatory support require MRI-compatible ventilators and monitors. Patients with surface EEG electrodes (e.g., those on continuous EEG

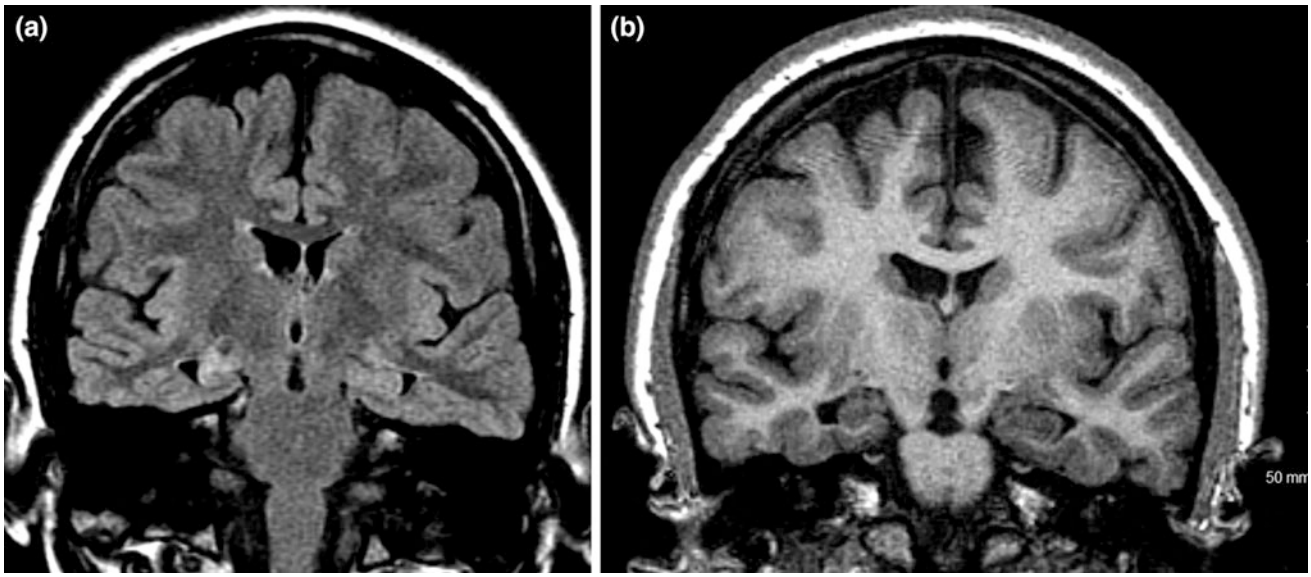

Fig. 6.2 Magnetic resonance imaging (*MRI*) scan of an 18-year-old woman with a history of seizures presenting in nonconvulsive status epilepticus. Coronal fluid attenuated inversion recovery (*FLAIR*)-weighted images show high signal intensity in the right hippocampus **(a).** Coronal spoiled gradient echo images show atrophy of the right anterior hippocampus **(b)**

monitoring) who require urgent imaging must be confirmed as having MRI-compatible electrodes first. Others patients have MRI performed prior to or after monitoring.

While most standard screening MRI examinations of the brain are sufficient to evaluate gross pathology, subtle pathology (which is now more often recognized in epilepsy patients) is seen only with high-resolution MRI studies that include thin-section isotropic 3-D spoiled gradient T1-weighted images, ideal for evaluating cortical morphology and the gray-white matter interface.

The exquisite resolution of images and multiplanar capabilities of MRI provide a significant advantage in evaluating seizure patients. Tumors, infection, or inflammatory lesions can cause seizures and epilepsy and are often seen readily by MRI, and the extent of surrounding edema and mass-effect can be seen easily as well. Developmental or structural disorders are best detected by MRI, including large structural deformities such as schizencephaly and lissencephaly, as well as more subtle heterotopias and cortical malformations (although visualizing the latter abnormalities may not be possible during an episode of SE). Many advantages of MRI are compromised in the setting of SE by clinical emergencies delaying time-consuming scans—and they cannot usually be done at all during GCSE.

Many epileptogenic lesions can be detected by changes in signal intensities; fluid attenuated inversion recovery (FLAIR) and T2-weighted images have increased sensitivity for detecting such lesions. Some acute insults lead to restriction of water diffusion in the brain and are detected best with diffusion-weighted imaging (DWI) sequences, which provide information regarding the microstructure of the brain and diffusivity of water in the local environment. Some of these findings were evident in a patient with hippocampal sclerosis who presented in NCSE (Fig. 6.2).

With MRI becoming a more accessible diagnostic tool across many sites, there are now several retrospective studies demonstrating regional and global abnormalities associated with convulsive SE [2], most commonly including restricted DWI signals, reduced T1-weighted signals, and sometimes, contrast enhancement [3–6]. Usually, at least one post-contrast imaging sequence should be obtained to detect contrast-enhancing lesions. There are fewer studies evaluating MRI changes in NCSE, but imaging findings are generally similar to those in convulsive SE. Bauer and colleagues reported T1-weighted changes and edema in the right frontal lobe in the patient who, at that point, had been in NCSE for 5 days [1]. In three patients with complex partial SE, Lansberg and colleagues demonstrated reversible cortical DWI and FLAIR abnormalities, similar to those seen in strokes, but not respecting vascular territories [7]. The abnormalities resolved, but some atrophy resulted in the same areas. Similarly, Chu and colleagues reported the case of a 52-year-old patient in NCSE whose MRI demonstrated marked cortical DWI hyperintensity throughout the brain, with an apparent diffusion coefficient (ADC) decreased in the corresponding areas [8].

Kawai and colleagues described a patient who presented in hypoglycemic coma with focal motor SE whose MRI showed multiple areas of signal hyperintensities broadly over the right hemisphere [9]. PET showed intense glucose hypermetabolism. After seizures ceased, the hyperintensities resolved, and atrophy was noted in some of those areas.

Much of the hippocampal atrophy found on long-term follow-up MRI scans has been the result of prolonged convulsive SE rather than NCSE and often in children, with both febrile SE and SE from other causes [10].

Transient peri-ictal MRI abnormalities have been reported in up to 30% of patients presenting in SE. In one series, the abnormalities (mostly increased T2, FLAIR, and DWI signals) were markedly varied in location, both cortical and subcortical, and in many regions [11]. At long follow-up (mean 30 months) 63% of patients had persistent MRI abnormalities, including focal atrophy and cortical laminar necrosis, but some of these abnormalities may have been related to the underlying causes of the SE. In another report, 19 of 69 patients (28%) presenting in the emergency department with focal or generalized SE, almost always convulsive, had peri-ictal DWI restriction, usually cortical, and most with additional thalamic DWI restriction; all patients with DWI restriction had periodic lateralized epileptiform discharges on EEG and had intense, repetitive seizures [12].

In some patients, cortical (with or without subcortical) T2 and FLAIR hyperintensity may resolve after seizures are controlled. DWI changes described in patients with focal motor SE often resolve. In others, irreversible brain injury can occur. The acute signal changes seen with hypterintense T2 or FLAIR and restricted diffusion may resolve, but encephalomalacia or cortical laminar necrosis can result in other patients [2]. Predicting the evolution of those lesions induced by seizures remains difficult.

Positron Emission Tomography

PET typically utilizes 2-deoxy-2-(18F) fluoro-D-glucose (FDG) in the interictal state to demonstrate the hypometabolic activity of epileptogenic regions. PET lacks the anatomic resolution of MR but, as it is a functional metabolic study, it can be more sensitive in detecting potential epileptogenic areas. Furthermore, EEG can be recorded simultaneously with PET, improving its diagnostic potential. Unfortunately, the availability of PET is limited and it is very costly. A PET scan takes approximately an hour to complete, including the administration and uptake of the agent and scanning time. PET scanning is typically ventilator-compatible, but trained personnel must be present to monitor neurologic and medical stability during the procedure.

FDG-PET changes described in case reports during NCSE have been inconsistent. Most reports on PET during SE have been with focal SE and have shown regional hypermetabolism [13]. One report demonstrated focal, regional, or multiregional hypermetabolism, which may correspond to the localization of EEG ictal activity [14]. In a patient with cognitive deficits, van Paesschen and colleagues found parietal hypermetabolism on PET scan, supporting the diagnosis of focal NCSE, while nearby frontal hypometabolism corresponded to focal slowing on the EEG, in turn correlating well with additional clinical deficits [15]. In other reports, focal hypometabolism was seen in the presence of NCSE due to a destructive lesion [16]. Handforth and colleagues found an area of hypermetabolism on PET in a patient with periodic lateralized epileptiform discharges on EEG following a focal-onset convulsion and concluded that this was evidence of ongoing focal NCSE [17]. Given the paucity of systematic studies, the role of PET in the diagnosis or treatment of NCSE has not been defined.

Single-Photon Emission Computerized Tomography

SPECT is an imaging test assessing blood flow to the brain. A radioactive tracer, typically 99Tc-EDC, is injected intravenously and then detected using a dual-headed scintillation camera and a high-resolution collimator. Often, ictal and interictal imaging are obtained, with the interictal image subtracted from the ictal image to identify the areas of ictal hyperperfusion. SPECT images can be obtained as soon as 15–30 min after injection but can be delayed up to several hours if necessary. Scan time is typically 15–25 min, and SPECT is ventilator-compatible. Concurrent EEG may be obtained, but depending on protocol used, there is a risk for electrode attenuation artifact on the SPECT images. Co-registration of SPECT to MRI can be very helpful in localizing seizure foci [18]. As with PET, ictal SPECT imaging itself poses no risk to the patient, but trained personnel must monitor the patient's medical and neurologic stability in cases of SE. A major practical constraint is that the radioisotope must be injected within several seconds of the start of the seizure [1, 18, 19].

There are several published reports of the utility of ictal SPECT in SE. Most are isolated case reports [13, 20, 21], and almost all describe SPECT changes in convulsive SE. In three separate studies with multiple patients, SPECT imaging showed increased focal or regional ictal perfusion in NCSE [13, 20, 21].

Tatum and colleagues reported that of seven patients with confirmed diagnoses of focal SE who underwent SPECT scans during the SE, six had areas of clear focal hyperperfusion [22]; the other patient had stopped having seizures 24 h prior to the SPECT scan—which showed focal hypoperfusion. Six other patients in whom a clinical suspicion of NCSE was considered initially but later disproved had no focal changes on SPECT.

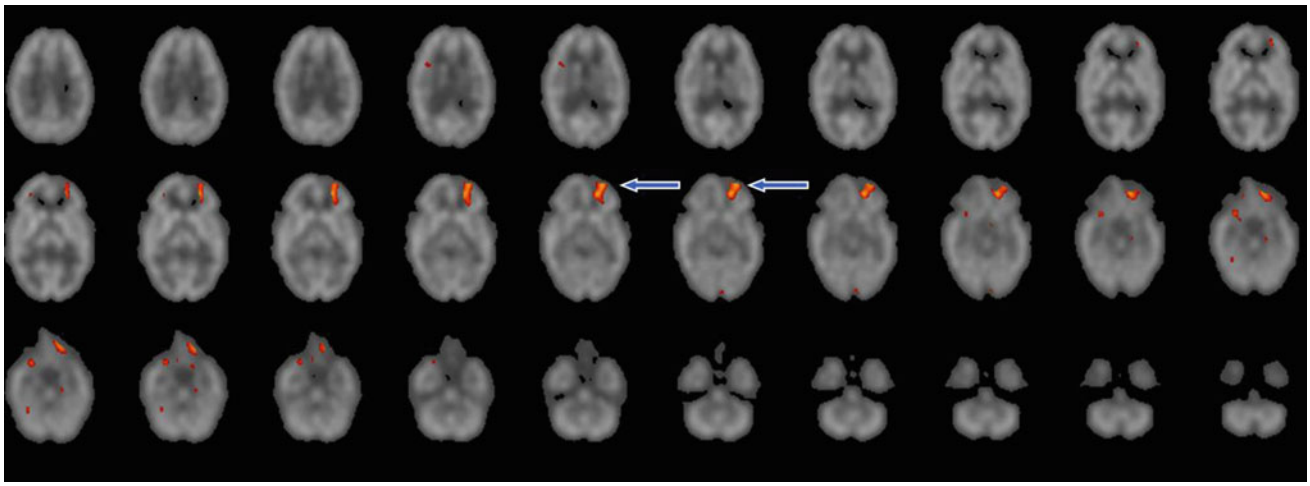

Fig. 6.3 Ictal single-photon emission computerized tomography (SPECT) image of 17-year-old girl with focal nonconvulsive status, with mild behavioral changes but no motor manifestations. Images show intense focal hyperperfusion in the left frontal lobe. (From Kutluay et al. [23], with permission)

Kutluay and colleagues evaluated the diagnostic and localizing value of ictal SPECT in three patients with NCSE [23]. All had ictal scans from which interictal scans were subtracted digitally, and all three demonstrated a well-localized increase in cerebral perfusion (Fig. 6.3).

Five patients with NCSE of frontal origin who underwent ictal SPECT were reviewed by Thomas and colleagues [19]. NCSE was caused by several different etiologies. Injection was performed within 10 s of seizure onset, with the SE treated with benzodiazepines after another 10 min. SPECT scans were then acquired 45–60 min after SE was terminated. All five studies showed regional hyperperfusion and were considered very helpful in seizure localization.

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Part II
Convulsive Status Epilepticus

Causes, Manifestations, and Complications of Generalized Convulsive Status Epilepticus in Adults

7

Raoul Sutter, Tolga D. Dittrich, and Peter W. Kaplan

Epidemiology and Socio-economic Impact

Generalized convulsive status epilepticus (GCSE) is a common and life-threatening neurologic emergency and represents a frequent epileptic condition across most age groups [1–3], with an annual incidence rate between 6 and 41 per 100,000 people [4, 5]. The incidence of GCSE has a characteristic bimodal age distribution pattern, peaking in infancy and in elderly patients (>60 years) [3, 6–8]. (See also Chap. 3, "The Epidemiology of Status Epilepticus".)

Status epilepticus (SE) in general, and refractory GCSE in particular, are associated with high morbidity and mortality rates and the necessity for costly neurointensive care, and they require treatment of both neurologic and systemic complications [9–13]. Aside from the etiology of SE, the seizure type at SE onset has been recognized as a main outcome predictor, with convulsive seizures being associated with the second highest mortality rate—after nonconvulsive SE (NCSE) in coma [14]. Mortality associated with GCSE ranges from 3 to 40% across various studies [9, 13, 15–17]. One study of the prognostic value of clinical features at SE onset integrated the different types of SE (group 1: simple partial, complex partial, or absence SE; group 2: GCSE; group 3: nonconvulsive SE in coma), age, seizure history, and level of consciousness into a scoring system for prognosis after SE, the Status Epilepticus Severity Score, or STESS [18]. This clinical outcome score had 100% sensitivity for prediction of death, with specificity of 64%. In a first validation of the scoring system, NCSE in coma and GCSE were the only SE types with a significant association with fatality [19].

In a systematic review of the costs of SE, the estimated mean inpatient costs per admission totaled up to $18,834 in the USA and €8347 in Germany, with an average length of stay of 13 and 14 days, respectively [20]. The mean annual direct costs for SE have been estimated at 4 billion US$ in the USA and at 83 million € in Germany, with acute central nervous system (CNS) etiologies as the major cost-driving factors. A recent study of the treatment costs of SE showed that refractoriness to first-line antiseizure medication and the need for mechanical ventilation were the main cost-determining factors [21].

Clinical and Electroencephalographic Manifestations

Generalized convulsive SE is characterized either by continuous generalized tonic–clonic convulsive seizures of more than 5 min, or by repetitive bilateral convulsive seizures without interictal recovery to functional baseline [22]. Typically, each convulsion begins with tonic stiffening, either focal or generalized, followed by clonic jerking of the involved muscles, increasing in amplitude and decreasing in frequency over time. The average duration of the initial tonic and clonic phases is about 90 s, but tends to shorten with each subsequent seizure as GCSE progresses. Although GCSE can be preceded by partial seizures or partial SE and convulsions typically decrease in frequency and intensity over time, generalized clonic movements represent the pathognomonic clinical feature of GCSE. Further characteristic signs of GCSE include mental status impairment (coma, lethargy, or confusion), and patients with GCSE may have focal neurologic deficits in the postictal phase, i.e. a "Todd's paralysis," a focal neurologic deficit lasting hours to days after convulsions.

R. Sutter (✉)
Department of Neurology and Intensive Care Medicine, University Hospital Basel, Petersgraben 4, Basel, BS 4021, Switzerland
e-mail: raoul.sutter@usb.ch

T.D. Dittrich
University Hospital Basel, Petersgraben 4, BS 4031 Basel, Switzerland
e-mail: tolga.dittrich@usb.ch

P.W. Kaplan
Department of Neurology, Johns Hopkins Bayview Medical Center, 4940 Eastern Avenue, 301 Building, Room 2115, Baltimore, MD 21224, USA
e-mail: pkaplan@jhmi.edu

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Table 7.1 Five identifiable electroencephalography (EEG) patterns often occurring in a predictable sequence during the course of generalized convulsive status epilepticus

The sequential EEG patterns	Definition of EEG patterns
1. Discrete seizures	Focal low-voltage fast activity which increases in amplitude, spreads across the midline, and then slows in discharge frequency. Generalized muscle artifacts during the tonic seizure are followed by periodic muscle artifacts as the tonic activity converts to clonic jerks. With the end of the last clonic jerk, low-voltage slow activity appears and continues until the development of the next discrete seizure.
2. Merging seizures with waxing and waning amplitude and frequency of EEG rhythms	Rhythmic but frequently asymmetric sharp wave or spike/wave patterns with recurrent build-up and subsequent slowing of frequency and waxing and waning of amplitude. There is no intervening low-voltage slow activity, as in the discrete seizure pattern. The rhythmic build-up is sometimes associated with overt generalized seizures. More commonly focal intermittent tonic and/or clonic convulsive activity is seen.
3. Continuous ictal activity	Rhythmic, relatively constant and frequently asymmetric, sharp wave or spike/wave discharges. Such discharges are associated with either continuous generalized clonic jerks, or only subtle clonic movements. Rarely, only diffuse, continuous, rhythmic slowing appears during status.
4. Continuous ictal activity punctuated by low-voltage 'flat periods'	The continuous ictal discharges described in continuous ictal activity can be punctuated by brief (0.5–8 s) episodes of generalized flattening on the EEG. Although the epileptiform discharges sometimes were asymmetric, the flat periods are always generalized. This EEG pattern can be associated with overt or subtle focal clonic movements or no motor symptoms at all.
5. Periodic discharges on a suppressed background	Bilateral, sometimes asymmetric, high-voltage, monomorphic, repetitive sharp waves on a relatively flat background. This can rarely be the initial pattern, and can also be seen in partially treated patients before status is completely controlled.

From Treiman et al. [27]

Initial generalized tonic and clonic movements have been termed "overt" SE [23]. In later stages of GCSE, there may be an electroclinical dissociation in which there is ongoing seizure activity on the electroencephalography (EEG), but little if any clinical correlate. This is termed "subtle" SE [24]. After GCSE has transformed into subtle SE (with less prominent and specific signs of seizures, such as slight twitching of the limbs or facial muscles, or jerking eye movements) there may even be coma without other signs of seizures. The first description of "subtle" SE by Treiman and colleagues as a syndrome of subtle clinical signs and continuous or nearly continuous, usually bilateral, epileptic EEG patterns [24] was subsequently expanded to include the evolution of a single convulsion into subtle SE, rather than to convulsive SE. Although most subtle SE presents with focal components at some point, periodic discharges usually become bilateral even if initially occurring unilaterally [23].

In order to diagnose the persistence of (often-missed) "subtle" SE, EEG is recommended in patients with prolonged and unexplained altered level of consciousness after overt seizures have stopped, or if there is no (or incomplete) return to the patient's prior baseline after initial antiseizure therapy [25]. The EEG is also helpful in further distinguishing true GCSE with generalized seizures at onset from SE with initial partial seizures, which may generalize secondarily [26].

A contribution to a better understanding of EEG changes during different stages of untreated GCSE was made by the description of a progressive sequence of five EEG patterns by Treiman and colleagues (Table 7.1), published before widespread use of continuous EEG (cEEG) monitoring [27]. This evolution underscores the importance of cEEG in the management of GCSE. Other investigators, however, have not found this sequence of EEG patterns [28–30]. Furthermore, especially in epilepsy monitoring units, the EEG may help by demonstrating nonepileptic patterns in patients with psychogenic seizures or pseudostatus epilepticus.

Etiology

The underlying causes for GCSE are diverse and cannot be determined in up to a third of subjects [16]. Nonetheless, there is a large range of well-studied factors that can lead to GCSE. Etiology is recognized as the most important prognostic factor (see Chap. 10). Studies of the clinical impact of SE etiology face several challenges, not least because in early studies, agreement on definitions of epilepsy and acute seizures was lacking. Also, etiologic classifications promulgated by the International League Against Epilepsy (ILAE) for seizures and epilepsy syndromes [31] were not

applied, or were used incorrectly. Hence, variations in analyses of risk factors, etiologies, and outcome predictors in SE and GCSE have led to confusion, and epidemiologic measures are often misstated. Subsequently, the ILAE Commission on Epidemiology and Prognosis has established guidelines for epidemiologic research in epilepsy [31], classifying SE into acute symptomatic, remote symptomatic, progressive symptomatic, idiopathic, or cryptogenic types, based on determination of the underlying etiologies.

In general, two main etiologic groups of GCSE can be differentiated: GCSE on the basis of a known epileptic seizure disorder and GCSE as a consequence of (in decreasing frequency) earlier cerebrovascular disease, degenerative disorders, or metabolic, hypoxic, or infectious illnesses. In a systematic review of the frequency and outcome of GCSE, the most common underlying causes were cerebrovascular disease and low antiseizure drug levels [4].

In a population-based study in Virginia [1] and other investigations in SE [13], patients with anoxia or with several comorbidities have the highest mortality rates. Patients with other acute etiologies such as ischemic strokes, tumors, and traumatic brain injury, have an intermediate mortality rate. Alcohol-related GCSE seems to have an intermediate or low mortality, and patients with previous epilepsy in whom GCSE develops due to an exacerbating factor generally have the lowest mortality [4, 13].

According to a recent study of 126 patients with GCSE, acute symptomatic etiology was found in 59% [15]. Patients with treatment-refractory GCSE had a higher proportion of underlying CNS infections than patients with nonrefractory GCSE (44.4% vs. 23.5%), and notably, viral encephalitis was significantly more common in refractory GCSE than in nonrefractory cases (31% vs. 6.2%).

Less frequent but still significant etiologies of GCSE are: uncontrolled epilepsy, intoxication (especially with alcohol and illicit drugs), brain tumors, and traumatic brain injury [1, 6, 16, 32]. Table 7.2 presents the causes of GCSE in relation to outcome in patients with and without epilepsy.

In critically ill patients, myoclonus is observed frequently and often raises concerns for underlying seizures or SE, but some types of myoclonus do not represent or end in seizures. While myoclonus generated from subcortical, spinal, and peripheral sites usually does not transform into seizures, cortical myoclonus can convert into seizures and GCSE regardless of etiology [33, 34]. There is evidence that the antiepileptogenic potential or effectiveness of the most frequently used drugs, such as diazepam, lorazepam or phenytoin may vary especially in the context of symptomatic seizures [35] and that treatment directed towards the underlying etiology can be key to seizure control.

Prior Epilepsy

One of six patients with epilepsy will suffer from at least one episode of SE in the course of a lifetime [8, 9]. Almost half of patients with SE and known epilepsy have already had a previous episode of SE [3]. According to different studies, the proportion of patients with SE who have previously known epilepsy ranges between 40 and 70% [1, 3, 36, 37].

In patients with GCSE, there is a prior history of epilepsy in more than two-thirds of cases [16]. Mortality in patients with GCSE and a history of epilepsy is 6% [16]. SE in adults is rarely the initial manifestation of epilepsy [3, 8, 36]. In particular, elderly SE patients usually have no seizure history [1, 3].

While NCSE in the form of absence or complex partial SE usually occurs in patients with known epilepsy [32], GCSE commonly emerges in association with causes other than prior epilepsy, such as with trauma, cerebrovascular, metabolic, anoxic or neoplastic insults, even in patients with known epilepsy [16]. Interestingly, there are differences in outcome between GCSE patients with and without an underlying epileptic disorder: patients with earlier epilepsy had favorable neurologic outcomes in over 80% of cases, and a mortality of <10% [16], while patients without

Table 7.2 Etiology of generalized convulsive status epilepticus in relation to outcome in patients with and without epilepsy

Etiology of generalized convulsive status epilepticus	Outcome		
	Favorable	Increased morbidity	Increased mortality
Prior epilepsy	+++	+	+
Acute symptomatic	+	++	++ +++ for hypoxic brain injury
Remote symptomatic	++	+	+
Progressive neurologic disease	++	++	+
Unknown	+++	++	+

Tentative grading of different outcomes by the authors
+ minor
++ moderate
+++ strong

reported epilepsy had favorable outcomes at discharge in less than 60% of cases, with a mortality exceeding 20% [16].

In patients with known epilepsy and no acute structural brain insult, several different scenarios may trigger GCSE. Alcohol use or withdrawal, intercurrent illness, sleep deprivation, and noncompliance with antiseizure medication appear to be the most common [1, 16]. Although many cases of GCSE in epilepsy patients are due to antiseizure drug reduction or withdrawal [4], acute neurologic diseases should also be considered in this context; cerebrovascular insults, CNS infections, or traumatic brain injury can be precipitants or causes for GCSE in patients with epilepsy [3, 16].

Acute and Remote Neurologic Illness

Cerebrovascular Disease. Strokes (either ischemic or hemorrhagic) are an uncommon but serious precipitant of GCSE, accounting for up to 20% of all types of SE [36, 38, 39]. In patients with GCSE, acute strokes are the precursor in 8% [16]. In the elderly, in whom vascular disease is more common, strokes account for >50% of SE and should be sought as the cause [1, 9, 32, 40, 41]. SE after strokes is usually categorized according to the time between the stroke and SE onset: "early-onset" SE emerges within 7 days of the stroke; "late-onset" SE occurs at least 8 days after the stroke. Early-onset SE following stroke has a prevalence between 2 and 6% of patients with SE. In a study of SE following acute stroke, ischemic and posterior cerebral artery strokes were the most frequent stroke types in patients with late-onset SE, while stroke types were evenly spread among patients with early-onset SE [41]. Of 121 patients in one study, post-stroke SE occurred in 30 patients with SE (24.8%), and 30% of SE was GCSE. In the early-onset SE group, however, NCSE was more common than GCSE. Another study showed that SE more commonly occured in stroke patients with higher disability scores, with 9% of post-stroke seizure patients having SE. In that study, the risk of SE was not associated with type or cause of stroke, or with lesion size or cortical involvement [38]. In a study using the US Nationwide Inpatient Sample over an 8-year period with 718,531 hospitalizations for acute ischemic stroke, 1415 patients (0.2%) developed GCSE [42]. Of 102,763 patients admitted to hospital with intracranial hemorrhage, GCSE developed in 266 (0.3%). In-hospital mortality was significantly higher in those with GCSE and acute ischemic stroke or intracranial hemorrhage [42].

In contrast to subarachnoid hemorrhage, intracerebral hemorrhage (ICH) led to a significant risk of early-onset seizures [39]. ICH-related SE can be seen in up to 20% of patients [42–44]. Cortical involvement and hemorrhagic transformation of an ischemic infarct were predictive of early seizures [45, 46]. SE is a potentially lethal complication of acute stroke, but early seizures are not clearly associated with increased mortality [39, 46–51]. A study analyzing the types of stroke-related SE showed that NCSE was the predominant SE type in the early-onset group and frequent in the late-onset group, underscoring the need for clinical awareness and the importance of EEG monitoring in stroke patients with altered levels of consciousness, especially in the early post-stroke phase and even in the absence of convulsions [41].

Brain Tumors. Status epilepticus can originate from a variety of cerebral tumors, with inconsistent impact on morbidity [36, 52, 53]. There are scant data regarding the incidence and prevalence of GCSE linked to brain tumors, and most derive from cohorts with a large variety of types and locations of tumors. In a review of malignant gliomas, tumor-related SE was often refractory but was not generalized convulsive in type [52]. Primary brain tumors are more likely to generate focal SE than GCSE [4]. Conversely, a large epidemiologic study identified tumors accounting for almost 2% of GCSE [6]. Another large epidemiologic investigation found brain tumors linked to 7% of all SE [54]. Patients with brain tumor-related epilepsy appear less likely to develop tumor-associated SE than are other epilepsy patients to develop SE [53]. Tumor-associated SE occurs more commonly when the tumor is in the frontal lobes. In contrast to tumor-associated epilepsy, where seizures commence early in the course of the disease, tumor-associated SE more often appears later. In patients with malignant gliomas, seizures are common, in 20–40% at presentation, and patients with seizures at presentation appear to have a greater risk of subsequent SE [52].

Head Injuries. Craniocerebral injuries are responsible for up to 26% of all types of SE [55], but this may include both remote and acute traumatic brain injuries (TBI). In up to 10% of patients with GCSE, TBI is thought to be the main etiology [16]. The risk of seizures after TBI correlates with the severity of the trauma and the time since the injury. Even unprovoked seizures emerging several years after serious injuries may be attributable to the trauma, but data from several studies suggest that mild TBI accompanied by a brief episode of unconsciousness or amnesia (but not associated with significant brain contusion, intracranial hematoma, or fracture) does not increase the risk of posttraumatic seizures [56–58].

Numerous studies have examined the effectiveness of posttraumatic antiseizure prophylaxis. There is evidence that antiseizure medication reduces early symptomatic seizures effectively, but a favorable impact on mortality was not detected [35, 59]. Also, the development of late posttraumatic seizures and SE cannot be prevented by prophylactic administration of antiseizure drugs [35, 60]. Further studies are needed to clarify if early and intensive seizure suppression may improve long-term outcome in this population.

Metabolic Disorders. Acute metabolic derangements account for 11.5% of all causes of SE in general, and SE with this cause has a mortality of about 30% [61]. Acute metabolic derangements are the presumed causes of about 4–26% of SE [13, 62–64], with a mortality of up to 25% [64]. Patients with acute metabolic disorders and GCSE were significantly more likely to require mechanical ventilation, and patients who required mechanical ventilation had a 7.43% mortality, compared to 2.22% for those who did not [17].

Systemic Illness

Infection and Inflammation. Meningitis and encephalitis are relatively rare causes of GCSE. In two large population-based series, primary CNS infections accounted for only 0.6% and 3% of SE in general [6, 54]. In a study of patients with GCSE, encephalitis and meningitis were the presumed underlying etiology in 3% [16]. Diagnosis of CNS infections in patients with GCSE can be challenging because patients may have blood and cerebrospinal fluid leukocytosis unrelated to an underlying infectious disease [36]. Peripheral leukocytosis is often caused by the demargination of white blood cells as a consequence of SE.

The mechanisms of neuronal damage and further seizure promotion are closely related to the immune response to pathogens, mediated by the release of cytokines. In brief, clinical and experimental studies have uncovered several mechanisms as integral parts of a bidirectional relationship between SE and inflammation. Systemic and local inflammation caused by SE and CNS infection or inflammation, or the cytotoxic effect of accumulation of the neurotransmitter glutamate as the result of ongoing seizures may contribute to sustaining SE [65–67]. Systemic inflammatory reaction induced by prolonged seizures is mirrored by increased serum cytokine levels, circulating immune cells, and the disruption of the blood–brain barrier (BBB) [67, 68] independent of infections [69]. Altered BBB increases the permeability for ions and proteins, facilitating transmigration of inflammatory cells that contribute to sustained seizures [70]. Furthermore, cytokines that promote the release of neuroactive molecules (e.g., glutamate, nitric oxide, neurotrophins) from glia or the endothelium [71, 72] or activate neuronal receptors in the CNS may modulate neuronal activity [73, 74].

Infectious Encephalitides. Data regarding GCSE associated with infectious encephalitis are scant. In one study of 236 GCSE patients, encephalitis or meningitis was diagnosed in 7% [16]. Other series have very limited sample sizes, so further characterization of patients with GCSE and infectious encephalitides is lacking. In another study of prognosis and predictors of outcome of refractory GCSE, viral encephalitis was significantly more common in refractory SE than in nonrefractory SE [15], confirming the findings of another study of GCSE treatment in which viral encephalitis was associated with treatment refractoriness [75].

Autoimmune Encephalitides. Along with the recent increased interest in antibody-mediated autoimmune encephalitis, current investigations often focus on the analysis of immune-mediated SE, but data regarding GCSE associated with autoimmune encephalitis in adults are scarce. Seizures in patients with multiple sclerosis (MS) are more frequent than are seizures in the general population [76, 77]. Partial-onset seizures are likely related to the focal or multifocal nature of the subcortical demyelinating lesions. In contrast, GCSE related to MS appears to be rare—with about 1% of patients with GCSE having MS [6, 16]. In a review of 268 MS patients, one of 20 patients with seizures had GCSE [76]. In contrast, in a large study of more than 5000 patients with MS, 1% had seizures, and GCSE was not detected [77]. While focal motor SE can be a serious complication of MS, GCSE appears to be rare.

Another treatable form of autoimmune encephalitis sometimes accompanied by refractory GCSE is characterized by antibodies against the $GABA_A$-receptor. In a study analyzing serum and cerebrospinal fluid (CSF) samples of 140 encephalitis patients with seizures or SE, high titers of serum and CSF $GABA_A$-receptor antibodies were associated not only with severe encephalitis, but also with treatment-refractory GCSE; the mechanism is thought to be reduction of synaptic $GABA_A$-receptors [78]. The recognition of this disease is important, as it is potentially treatable and often occurs with GABA-ergic and other co-existing autoimmune disorders [79]. (See also Chap. 8, "Unusual Causes of Status Epilepticus".)

Intoxications. Alcohol is probably the toxin most commonly associated with GCSE. The immediate effect of ethanol is mediated by its interference with glutamate, increasing the binding of glutamate to N-methyl-D-aspartate (NMDA) receptors. Long-term abuse causes adaptive changes within the NMDA receptor and leads to inhibition. Homocysteine levels, which increase during alcohol intake, increase further during abrupt alcohol withdrawal, possibly promoting alcohol withdrawal seizures [80]. In addition, alcohol interferes with antiseizure medication by inducing liver metabolism, leading to more rapid metabolism of some antiseizure drugs [80]. Alcohol was identified as a potential trigger for SE in 13% of patients in one large population-based study [54], and chronic alcohol abuse was reported in more than 8% of cases in another population-based GCSE study [6]. In another study of 249 GCSE patients, 11% had alcohol abuse as the only identifiable SE trigger [81]. Most patients with alcohol-related GCSE recovered without new neurologic deficits [82]. Benzodiazepines are the most effective antiseizure drugs for the primary and secondary prevention of alcohol withdrawal seizures [83].

Overdose of several prescription drugs can result in SE (e.g., theophylline, isoniazid, amitriptyline, thioridazine, pentazocine, lithium, and baclofen) [36, 37], but data from large studies are lacking. Several recreational drugs, such as cocaine, amphetamine, and heroin are additional but rare causes of SE. Seizures may occur not only in association with chronic abuse but also with first-time intake [37, 84]. In contrast to NCSE [85], data regarding GCSE in relation to other intoxications are scarce.

Precipitants

The Range of Potential Provoking Factors

Distinguishing between causative and triggering factors of GCSE is often difficult. Acute strokes, for example, are serious events characterized by especially poor outcome compared to that of other etiologies and may cause SE in patients with or without prior seizures [37, 39]. In contrast, patients who develop SE in the context of alcohol withdrawal or an acute head injury are more likely to have a history of seizures [3]. These observations call for differentiating between precipitants and etiologic factors. Events that, in the absence of a predisposition, would presumably not have caused SE by themselves could be labeled as "precipitants" in association with an underlying epilepsy. Sometimes more than one acute precipitant can be present in a case of SE [3, 9]. The observation that patients with SE from an acute neurologic insult have a history of epilepsy more frequently than do those in the general population, suggests that a history of seizures accompanies these etiologic risk factors [3]. Furthermore, there is a change in the types of precipitants according to age; children more frequently have infections and fever [9, 86].

Precipitants in Patients with Epilepsy

In patients with epilepsy, some triggering risks are low antiseizure drug levels, sudden discontinuation of antiseizure medication or insufficient therapeutic dose adjustment, alcohol intake, and acute critical illness and fever [1, 16, 37, 87]. Nevertheless, the definite precipitant remains unknown in a third of patients [16].

Acute Neurologic and Systemic Complications

Acute manifestations and complications of patients with GCSE can be categorized as neurologic or systemic. While most neurologic manifestations of GCSE result from ictal or postictal brain dysfunction or both as a direct consequence of cytotoxic damage to glia and neurons during seizures or seizure-related brain inflammation, the clinician should also be aware of other causes including structural, infectious, and metabolic disturbances of the CNS.

Acute systemic complications are frequent and can have serious impact on the course and outcome of GCSE. Pathophysiologically, most acute systemic complications ultimately result from the persistence of generalized convulsions. Intense muscle contractions may lead to an increase in body temperature, increased serum potassium levels, a dysfunction of accessory respiratory muscles with resultant hypoxia, respiratory acidosis and, if prolonged, increased oxygen consumption, metabolic acidosis, and a dramatic decrease of adenosine triphosphate (ATP). Further, with increased muscle breakdown, serum concentration of creatine phosphokinase and myoglobin may increase dramatically, leading to acute kidney failure. Marked increase in plasma catecholamines can cause a decay of skeletal muscle cells and cardiac dysfunction [88], including stress cardiomyopathy [89]. Potentially lethal complications are those of a systemic nature, especially with metabolic, respiratory, and cardiac involvement [8, 16]. Figure 7.1 displays possible acute neurologic and systemic complications and their complex, often bidirectional, and self-sustaining interactions. Because of the complexity of these interactions, it can be difficult not only to identify the complications with the strongest impact on the course and outcome of GCSE, but also to distinguish complications attributable to the underlying etiology from the direct consequences of GCSE [8].

Acute Neurologic Manifestations

Acute Encephalopathy. Convulsions aside, acute brain dysfunction is a major feature of GCSE. The transient disturbance of neurotransmitters and cerebral metabolic homeostasis may lead to acute neuronal damage representing the principal pathological mechanism of SE-related acute ictal and postictal brain dysfunction (i.e., postictal encephalopathy; see Fig. 7.1). Acute neuronal damage in patients with prolonged GCSE is caused primarily by the cytotoxicity from increasing interstitial concentrations of excitatory neurotransmitters such as glutamate and aspartate [90–92]. Further, epileptogenesis and neuronal hyperexcitability may be increased by the activation and proliferation of astrocytes and microglia changing the neuronal architecture [69, 90, 93, 94]. In addition, underlying pathologic conditions, such as ischemic stroke, hypoxia, and infections may further promote the neuroglia activation [90]. Animal studies provide evidence that the neuroglia activation is accompanied by an increased release of cytokines, such as tumor necrosis factor alpha (TNF-α) and

interleukins, both associated with neuronal damage [93]. Moreover, astrocytes have an important role in the maintenance of the BBB as they are closely related to the endothelial cells and their tight junctions [90]. Increased astrocyte-mediated angiogenesis may also impair the normal function of the BBB, increasing its permeability by the release of cytokines [90, 95]. This mechanism may be paralleled by the activation of glutamate receptor subtypes on the surface of endothelial cells by the excessive release of glutamate, another contributing factor to the impairment of the BBB. The BBB breakdown, together with a drop in blood pressure after an initial episode of arterial hypertension during GCSE, leads to a significant dysregulation of cerebral circulation. Decreased cerebral perfusion, which does not meet the current metabolic cerebral demands, contributes further to the disruption of the BBB [92]. There is also a growing body of evidence that neurons, neuroglia, and endothelial cells in the CNS are capable of releasing cytokines themselves and may thereby contribute further to seizure-related brain inflammation [69].

Although there is no doubt that SE-related brain injury and subsequent acute encephalopathy result at least partially in and from CNS inflammation, it remains unclear to what extent neuronal injury is attributable to the seizure itself [94, 96, 97].

Besides seizure-induced brain inflammation, systemic hypoxia during GCSE plays an important role in accelerating seizure-related brain injury (see Fig. 7.1). Animal models with pharmacologically induced SE demonstrate that systemic hypoxia is not the only cause of seizure-related ischemic brain damage but also that hypoxia is a contributing factor, together with increased and disturbed neuronal metabolism [91, 96, 98]. Evidence was provided by Meldrum and colleagues using paralyzed, artificially ventilated baboons compared with nonparalyzed baboons [99]. For the same seizure durations, the observed neuronal damage was more severe in the nonparalyzed baboons, indicating that respiratory management and reduction of muscle action in patients with prolonged seizures and GCSE might reduce neuronal damage, and hence the acute encephalopathy [91, 98].

Acute Focal Neurologic Deficits—The Task of Distinguishing Structural from Nonstructural Genesis. The patterns of brain injury associated with prolonged seizures and their underlying mechanisms have been investigated well in animal models. Neuronal necrosis occurs in several cerebral areas such as the neocortex, hippocampus, basal ganglia, and the cerebellum [98]. Similar patterns of neuronal damage, including in the neocortex, hippocampus, thalamus, and cerebellum, have been described in children and adults dying shortly after an episode of GCSE [100, 101]. In a case-control study of neuronal loss in five hippocampal regions after GCSE in humans, DeGiorgio and colleagues identified the most severe neuronal loss in GCSE cases, and less cell loss in healthy controls, and in controls matched for age, hypoxia/ischemia, previous epilepsy, and alcohol abuse, suggesting a direct impact of GCSE on neuronal cell loss in humans [102].

Distinguishing acute focal neurologic deficits that result from structural or nonstructural causes is especially challenging in the early postictal state. In many cases it remains unclear to what extent acute neurologic deficits can be attributed to the SE itself or to the underlying structural lesions. This conundrum is especially evident in animal models where the substances administered to induce SE can also cause brain lesions and deficits. In patients with transient postictal focal neurologic deficits, the distinction between a Todd's paresis and persisting deficits from underlying structural brain lesions is challenging. Usually, postictal coma and neurologic deficits improve within minutes to hours, but recovery of neurologic function can take several days. Close clinical observation and appropriate brain imaging are essential for correct diagnosis and appropriate treatment. Finally, postictal impairment of movement by bone fractures during GCSE may mimic a Todd's paresis [103] and should be suspected in patients with prolonged weakness without lesions on brain imaging.

Acute Systemic Manifestations

Hypoxia. Systemic hypoxia occurs frequently in SE patients and is induced primarily by the impairment of ventilation and simultaneous increased oxygen demand during prolonged or recurring seizures, with the intense muscle contractions of GCSE. Hypoxia contributes significantly to the derangement of cerebral metabolism [98] and subsequent brain injury, usually resulting from a mismatch between substrate supply and demand in cerebral areas involved in the seizure [104]. During GCSE, compensatory factors are unable to meet the considerable metabolic demand of the seizing brain [104, 105]. Vulnerable brain regions may demonstrate hypoxic neuronal injury within 30–60 min after GCSE onset [104]. In this vulnerable phase, acute failure of cerebral oxygenation inhibits the Na^+–K^+ pumps of the neurons, leading to the loss of cellular integrity and further release of excitotoxic glutamate (see Fig. 7.1), followed by overstimulation of N-methyl-D-aspartate (NMDA) receptors. This overstimulation further increases cellular calcium loss, mediated by second messengers, and damage to the mitochondrial respiratory chain [106]. In this stage, the severity of injury depends on the duration and degree of respiratory or circulatory dysregulation or both, body temperature, and serum glucose levels. The increased glutamate-mediated

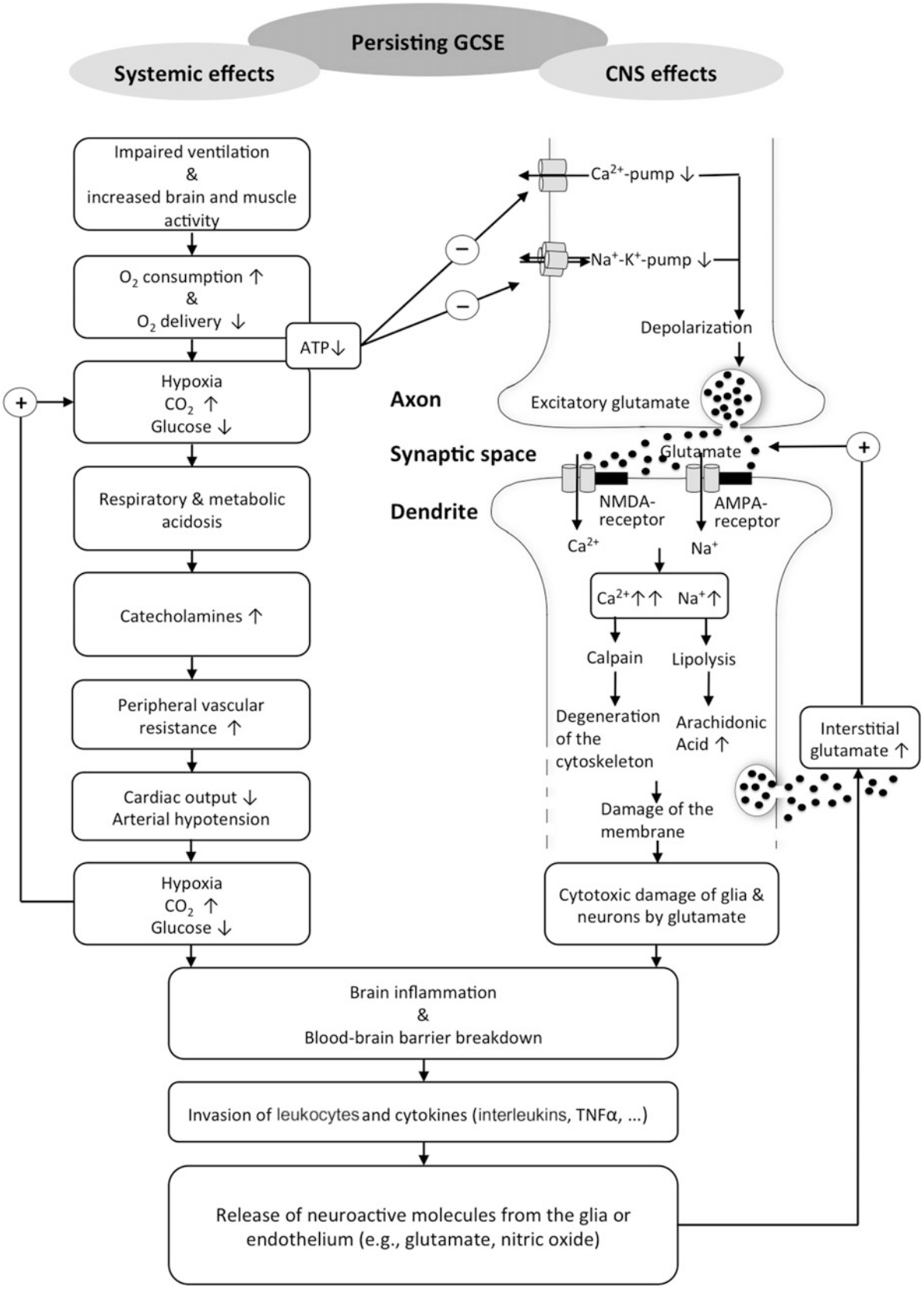

Fig. 7.1 Acute systemic and neurologic effects of generalized convulsive status epilepticus. CNS = central nervous system; ATP = adenosine triphosphate; TNF = tumor necrosis factors

excitatory neurotransmission and simultaneously decreased GABA-mediated neuroinhibition may further promote epileptogenesis and contribute to neuronal cell death.

Acidosis. Acidosis occurs in a large number of patients with GCSE. It consists of two components of particular relevance: first, the metabolic acidosis related to the accumulation of lactate, and second, the respiratory acidosis caused by the disturbance in breathing [107] (see Fig. 7.1). Arterial blood gas analyses in a study of mechanically ventilated patients with GCSE (and no overt prior metabolic derangements) showed that in the vast majority, arterial pH was below normal [36]. Serum pCO2 levels indicated both respiratory and metabolic acidosis, implying that impaired ventilation and the release of lactic acid into the bloodstream from ongoing convulsive muscle activity are important mediators of acidosis. In this study, however, acidosis was not associated with increased morbidity or mortality. Other than impaired ventilation and acute metabolic derangements (resulting from muscle contractions), there may be additional factors that contribute to acidosis in GCSE, such as drugs (e.g., salicylate poisoning by aspirin), intoxication (e.g., by ethylene glycol or methanol), or unrecognized prior underlying metabolic derangements (e.g., diabetic ketoacidosis, uremic acidosis, severe dehydration, or anemia with a lack of oxygen transport).

Cardiac Complications. Several hemodynamic effects can appear at an early or late stage of SE. As one of the first changes conditioned by the release of stress mediators (such as adrenaline and noradrenaline), the heart rate and mean arterial pressure begin to rise, with increase in peripheral vascular resistance [8]. As a result, cardiac output can decline (see Fig. 7.1) [8]. The impairment in ventricular function, characterized by reduced cardiac output and arterial hypotension, may result from the co-occurrence of hypoxia, prolonged seizure activity, and acidosis. With the excessive release of catecholamines, cardiac arrhythmias can occur and may even lead to sudden death in GCSE [108].

During GCSE, blood pressure tends to decrease further, in some cases leading to severe hypotension. Experiments in primates have shown that aortic pressures decline significantly within 45 min of onset of GCSE [108, 109]. Despite the changes described above, cerebral blood flow is still higher than usual but may be insufficient for brain needs.

There may also be therapy-related complications. Although the rationale for the use of anesthetic drugs in treatment-refractory GCSE seems clear, there are several *caveats*. Anesthetic drugs may contribute to cardiac and circulatory dysfunction, including cardiotoxicity with phenobarbital and pentobarbital, severe hypotension from thiopental [110], or cardiac failure from the propofol infusion syndrome (along with hepatotoxicity, metabolic acidosis, and rhabdomyolysis) [111]. Some recent studies of adults with SE raise concern about the safety of anesthetics in the treatment of refractory SE; they may be associated with increased morbidity and mortality independent of clinical confounders [112–114], although these three studies included all types of SE, so extrapolation to GCSE is not clear. These findings emphasize the importance of a careful clinical evaluation of the risks to patients associated with the use of anesthetic agents. Important risk factors were use of high doses of propofol (>5 mg/kg/h), sedation for more than 48 h, respiratory infection, catecholamine infusion, and high corticosteroid and catecholamine blood levels [10, 115].

Respiratory Complications. Respiratory impairment is a frequent, life-threatening complication of GCSE (see Fig. 7.1). Three major etiologic factors can be responsible for the worsening of respiratory function in GCSE: persisting muscle contractions that affect normal breathing activity; drugs commonly used for the treatment of GCSE with respiratory depressant effects, including benzodiazepines and anesthetics; and respiratory tract infections from aspiration due to impaired protective airway reflexes during GCSE.

Airway and respiratory management begins with a set of simple measures to avoid respiratory complications. Prior to intubation, the upper body should be elevated and head turned to the side in order to prevent aspiration. Airway patency (by oral or nasopharyngeal airway devices) must be assured given the risk of respiratory insufficiency and apnea. Sufficient ventilation and oxygenation must be maintained by the administration of oxygen or rapid intubation. Proper and immediate airway management and mechanical ventilation requires close, interdisciplinary management of GCSE patients in ICUs.

Rhabdomyolysis and Acute Renal Failure. Rhabdomyolysis has been reported frequently with prolonged GCSE, leading to myoglobinuria and acute renal failure [116]. The incidence of this complication may be lower recently with advances in neurointensive care and the use of pharmacologic neuromuscular blockade, but it occurs, often in association with hyperthermia [117]. Acute renal failure is due to the increased muscle activity of prolonged convulsions with subsequent rhabdomyolysis, as evidenced by increased muscle enzymes (e.g., creatinine phosphokinase) and myoglobinuria. Metabolic and hemodynamic changes due to decreased cardiac output and arterial hypotension can also lead to a nutrient supply shortage, acute tubular necrosis, and impaired kidney function. As discussed above [111], rhabdomyolysis, metabolic acidosis, and renal failure can also be provoked by extensive and prolonged use of propofol for GCSE [10].

Infectious Complications and Inflammation. Inflammatory and immunologic factors and their influence in the pathogenesis of SE have become prominent research fields [93]. The causative relationship between infections during SE and outcome needs further confirmation, but infections in patients with SE are common and often serious complications. They are associated with a higher risk for refractory

SE, more prolonged ICU stays, and higher mortality [118, 119]. In a study of the impact of infections in critically ill ICU patients, infections were diagnosed in 23% of those with SE, and 94% of infections were in the respiratory tract [118]. A higher proportion of patients with infectious complications died after the onset of SE compared to those without infections; those with infections also had more prolonged ICU stays and higher rates of treatment-refractory SE [118]—results confirmed in another study of patients with less severe types of SE [119]. These studies included all types of SE, and data regarding the impact of infections on the course and outcome of GCSE alone are lacking.

Even without infection, systemic inflammatory reaction can also be caused by seizures, and reflected by changes of cytokine levels (IL-1beta, IL-2, IL-6, and TNF-α), increases of circulating immune cells (neutrophils, lymphocytes, and natural killer-cells), and BBB disruption during SE [66–68, 120, 121]. The role of serum levels of C-reactive protein (CRP), procalcitonin (PCT), and white blood cells (WBCs) were analyzed at SE onset for reliability in diagnosing infections during SE [122]. Single WBC levels and CRP had low diagnostic reliability, whereas their changes over time correlated with the presence of infections [122].

The differential diagnosis of CNS infections is complicated. Episodes of SE can be accompanied by mild CSF pleocytosis, which can be mistaken for CNS infection [36, 107]. One study examined the predictive value of PCT for the presence of infections at SE onset, and for outcome. PCT levels at SE onset were not shown to be predictive, but they were independently associated with adverse outcome [123]. Also, systemic inflammatory responses may influence seizure activity and hence the course of SE [73, 124]. The synergy between inflammation and seizures is exacerbated by certain antibiotics, especially unsubstituted penicillins, fourth-generation cephalosporins, imipenem, and ciprofloxacin, especially in combination with renal dysfunction, brain lesions, and epilepsy—all common in patients with infections [125]. Still, the evidence for these interactions is modest, and prospective studies are needed to clarify whether in certain clinical scenarios (including GCSE) the antibiotics per se or underlying infection (with the release of proinflammatory cytokines) is the more important mediator for persistent seizures.

In patients with refractory SE, intravenous anesthetics for the induction of therapeutic coma, including midazolam, propofol, and barbiturates are also subjects of discussion regarding presumed adverse effects in patients with several types of SE [126]. Patients receiving anesthetic drugs for treatment of SE have a higher risk of death compared to those not receiving anesthetics independent of well known confounders [113], and sedated patients had more frequent drops in blood pressure requiring treatment with vasopressors (16% vs. 1.9%), and more infections compared to those not receiving anesthetics (43% vs. 11%). These results were found with patients with a mixture of SE types but may apply to those with GCSE alone. The lack of strong evidence for these adverse effects from randomized trials does not allow changes of the current recommendations for treatment of refractory SE with anesthetic drugs [126].

Hyperthermia. Hyperthermia is a treatable sequela of SE, along with cardiac arrhythmias, hypoxia, and acidosis [36]. Many patients develop an increase in core temperature during GCSE due to prolonged motor activity. The hyperthermia itself may ultimately lead to brain injury beyond its effects on cerebral metabolism [36, 91, 98]. In rat models, hyperthermia during SE, and with similar EEG findings during seizures, led to more severe hippocampal damage than occurred in normothermic counterparts at 24 h [127]. Data on the impact of hyperthermia on outcome in adult humans with GCSE are lacking.

Physical Injury. An event as violent as GCSE can lead to serious physical injuries. Understanding the incidence, types, and patterns of injuries is key to appropriate management and injury prevention and allows clinicians to screen GCSE patients for common injuries, especially if patients remain unable to communicate discomfort or pain. Reports of injuries in patients with GCSE are scarce, but there is information on injuries associated with convulsive seizures and they appear similar to those in GCSE. In video-EEG monitoring units, serious adverse events during monitoring occurred in about 10% of patients, including seizure-related falls, injuries, and fractures [103, 128]. Head injury is the most common seizure-related trauma [129], occurring in up to 50% of admissions for seizure-related injuries [130].

Intense muscle contractions during GCSE may cause fractures, especially in the proximal femur and proximal humerus, along with posterior dislocation fractures (especially in the shoulder), and thoracic vertebral body compression fractures [103, 131, 132]. In one study, fractures were diagnosed in 6% of patients with at least one seizure in the preceding year [129]. The most reliable predictors of developing a seizure-related fracture included seizure severity, epilepsy duration, prior progressive scoliosis, and drug-related adverse effects, including the effect of prolonged use of enzyme-inducing drugs on bone density [128, 132].

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Unusual Causes of Status Epilepticus

8

Nicolas Gaspard

Introduction

Often, finding the cause of status epilepticus (SE) is straightforward. Most neurologists are familiar with the common etiologies of SE, such as nonadherence or recent changes in anti-seizure treatment, alcohol withdrawal, acute or remote stroke, brain tumor, and toxic-metabolic disturbances [1–4]. These common causes are summarized in Table 8.1 and discussed elsewhere in this book.

In a substantial minority of frustrating cases, however, clinicians are unable to firmly ascertain the etiology of SE on the basis of the information obtained from the medical history and the initial work-up. In this scenario, which often involves a previously healthy young adult or child, a long list of diagnostic tests is typically ordered that will sometimes lead to the correct diagnosis [5].

Finding the cause of SE serves at least two major purposes: therapeutic and prognostic. The management of SE is unusual among neurologic disorders, as the initial treatment almost always focuses on the symptomatic control of seizures prior to determination and treatment of the underlying cause [6]. Prompt cessation of both generalized convulsive SE (GCSE) and nonconvulsive SE (NCSE) is associated with better outcome [7, 8]. Once seizures are terminated, however, and perhaps even more importantly if they persist despite intensive anti-seizure treatment, the treatment of the underlying etiology needs to be undertaken. Diagnostic and therapeutic delay contributes to poor outcome in a variety of conditions that can cause SE, such as viral or autoimmune encephalitides [9, 10]. Further, seizure control might only be achieved provided the underlying cause is treated. An increasing number of studies have shown that etiology is one of the strongest independent determinants of outcome after SE [11–13]. It is indisputable that SE due to an easily reversible systemic etiology (acute poisoning or withdrawal) is less likely to be associated with long-term disability or epilepsy than SE caused by an acute neurologic catastrophe. In some situations, SE might be the harbinger of a chronic neurologic disease, with long-term therapeutic and prognostic implications. New-onset status epilepticus might for instance represent the initial manifestation of a mitochondrial disorder [14]. Even if no specific cure is available, affected patients and families can be provided with early counseling and support once the diagnosis is made.

Virtually any neurologic disorder affecting the cerebral cortex can potentially result in seizures and SE. Indeed, more than 180 uncommon causes of SE have been reported [15]. They can be conveniently divided into four categories:

- Inflammatory and autoimmune encephalitis
- Uncommon infectious encephalitis
- Genetic and congenital disorders
- Toxin, drug, and intervention-related disorders

It is impossible to review every single cause of SE. Instead, we will focus on the clinical entities that can lead to SE as their initial or early manifestation and will pose a diagnostic challenge to the clinician. We will only briefly mention those that are likely to be known already at the time SE occurs, but some syndromes associated with a peculiar type of SE will be discussed.

Finally, it is important to recognize that in a few cases of de novo refractory SE, often preceded by a mild febrile illness, no clear etiology will be identified despite an extensive work-up. These cases have been described under several acronyms, including NORSE (new-onset refractory status epilepticus) in adults [16] and FIRES (febrile illness-related

N. Gaspard (✉)
Service de Neurologie et Centre de Référence pour la Prise en Charge de l'Epilepsie Réfractaire, Université Libre de Bruxelles – Hôpital Erasme, Route de Lennik 808, 1070 Brussels, Belgium
e-mail: nicolas.gaspard@erasme.ulb.ac.be

N. Gaspard
Neurology Department and Comprehensive Epilepsy Center, Yale University School of Medicine, 15, York Street LLCI 700, New Haven, CT 06520, USA

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Table 8.1 Common causes of status epilepticus

Stroke, including hemorrhagic
Low antiepileptic drug levels
Alcohol withdrawal
Drug withdrawal (benzodiazepine, barbiturate)
Anoxic brain injury
Metabolic disturbances
Infection (bacterial meningitis, herpes encephalitis, brain abscess)
Traumatic brain injury
Brain neoplasm
Remote brain injury
Febrile seizures (in children)

epilepsy syndrome) in children [17]. These entities and their possible etiology will be discussed. We will close the chapter by providing a practical approach to those difficult cases.

Inflammatory and Autoimmune Encephalitis

This category comprises a wide spectrum of disorders (Table 8.2), some of which have only recently emerged as causes of SE. In most recent series of encephalitis, autoimmune and inflammatory cases represented 8–22% of all causes [18–20]. Inflammatory causes represent only 2.5% of SE [21] but this proportion might be higher in patients with refractory SE [5, 22].

Paraneoplastic Limbic Encephalitis

Paraneoplastic limbic encephalitis is characterized by cognitive impairment, especially in memory; behavioral changes; seizures; and sleep disturbance [23]. Pathologic examination and brain magnetic resonance imaging (MRI) show evidence of inflammation in the limbic structures, particularly the mesial temporal lobes. In line with this preferential involvement, seizures are most often of the complex partial type, but they can generalize. Signs of wider involvement of the central and peripheral nervous systems, such as widespread encephalomyelitis, cerebellar degeneration, and sensory neuronopathy, are frequent, especially in the syndrome of diffuse encephalomyelitis associated with the anti-Hu antibody [24]. Hypothalamic dysfunction is a common feature of the encephalitis associated with Ma2/Ta antibodies and testicular cancer [25]. Status epilepticus as the initial or prominent manifestation of paraneoplastic encephalitis is uncommon but has been reported, mostly with the anti-Hu antibodies [5, 26–30].

CSF analysis is almost invariably abnormal, showing elevated protein levels and pleocytosis. The diagnosis is made by identification in the serum of one of the many known antibodies (see Table 8.2). The antibodies recognize intracellular antigens shared by the tumor and the neurons. They are not believed to play a direct pathogenic role and are mostly biomarkers. Neurologic involvement is attributed to a cell-mediated immune reaction. Paraneoplastic limbic encephalitis precedes the diagnosis of cancer in up to half of the cases. Its occurrence should prompt thorough and repeated investigations for an occult neoplasm, most frequently small cell lung carcinoma (see Table 8.2). Guidelines for the screening for occult malignancy have been published. Whole-body fluorodeoxyglucose positron emission tomography (FDG-PET) is superior to CT in demonstrating occult neoplasms [31]. A negative PET/CT scan does not rule out underlying cancer, and repeating a PET/CT scan after a 6-month interval is recommended, followed by screening every 6 months up until 4 years if testing remains unrevealing. Cases of seronegative paraneoplastic limbic encephalitis still occur and may cause SE. Whether or not this should justify a thorough investigation for an occult neoplasm in all patients with cryptogenic SE is unclear.

Response to immune therapies is often disappointing. Successful treatment of the underlying neoplasm is sometimes associated with partial neurologic improvement.

Encephalitis Associated with NMDA Receptor Antibodies

Although the clinical entity was described only 10 years ago [32] and the antibody discovered a few years later, the encephalitis associated with N-methyl-D-aspartate (NMDA) receptor antibodies has quickly emerged as the most common encephalitis associated with antibodies against a neuronal surface antigen [18–20]. In a recent publication from the California Encephalitis Project, it was four to five times more frequent than Herpes Simplex, Varicella Zoster and West Nile virus encephalitides, and as frequent as enterovirus encephalitis [33]. Most patients are young women but the syndrome can occur at any age [34]. A prodromal nonspecific febrile illness is common. It is followed a couple of weeks later by behavioral changes, short-term memory loss, delusions, and hallucinations. Seizures and SE mostly occur at this stage. They are most commonly of the generalized tonic-clonic type, but partial complex seizures have been reported. For an unknown reason, male patients tend to present more frequently with seizures at onset than female patients [35]. Status epilepticus can be refractory [5]. Patients then progress to a severe catatonic stage, during which they

Table 8.2 Inflammatory causes of status epilepticus

Paraneoplastic encephalitis	Anti-Hu
	Anti-Ma2/Ta
	Anti-Ri
	Anti-CV2/CRMP-5
	Anti-amphyphysin
	Seronegative
Autoimmune encephalitis	Anti-NMDA receptor
	Anti-VGKC complex (especially anti-LGI1)
	Anti-GABA(A) receptor
	Anti-GABA(B) receptor
	Anti-AMPA receptor
	Anti-glycine receptor
	Anti-GAD
Rasmussen encephalitis	
Multiple sclerosis, ADEM	
Steroid-responsive encephalopathy with autoimmune thyroiditis (SREAT)	
Primary angiitis of the CNS	
Systemic autoimmune disorder	Macrophage activation syndrome/hemophagocytic lymphohistiocytosis
	Systemic lupus erythematosus
	Sjögren (and anti-Ro/SSA)
	Thrombotic thrombocytopenic purpura
	Behçet syndrome
	Celiac disease

Abbreviations: *NMDA* N-methyl-D-aspartate; *VGKC* voltage-gated potassium channel; *LGI-1* leucine-rich, glioma inactivated 1; *GABA* gamma-aminobutyric acid; *AMPA* alpha-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid; *GAD* GABA decarboxylase; *PRES* posterior reversible encephalopathy syndrome; *ADEM* acute disseminated encephalomyelitis; *CNS* central nervous system

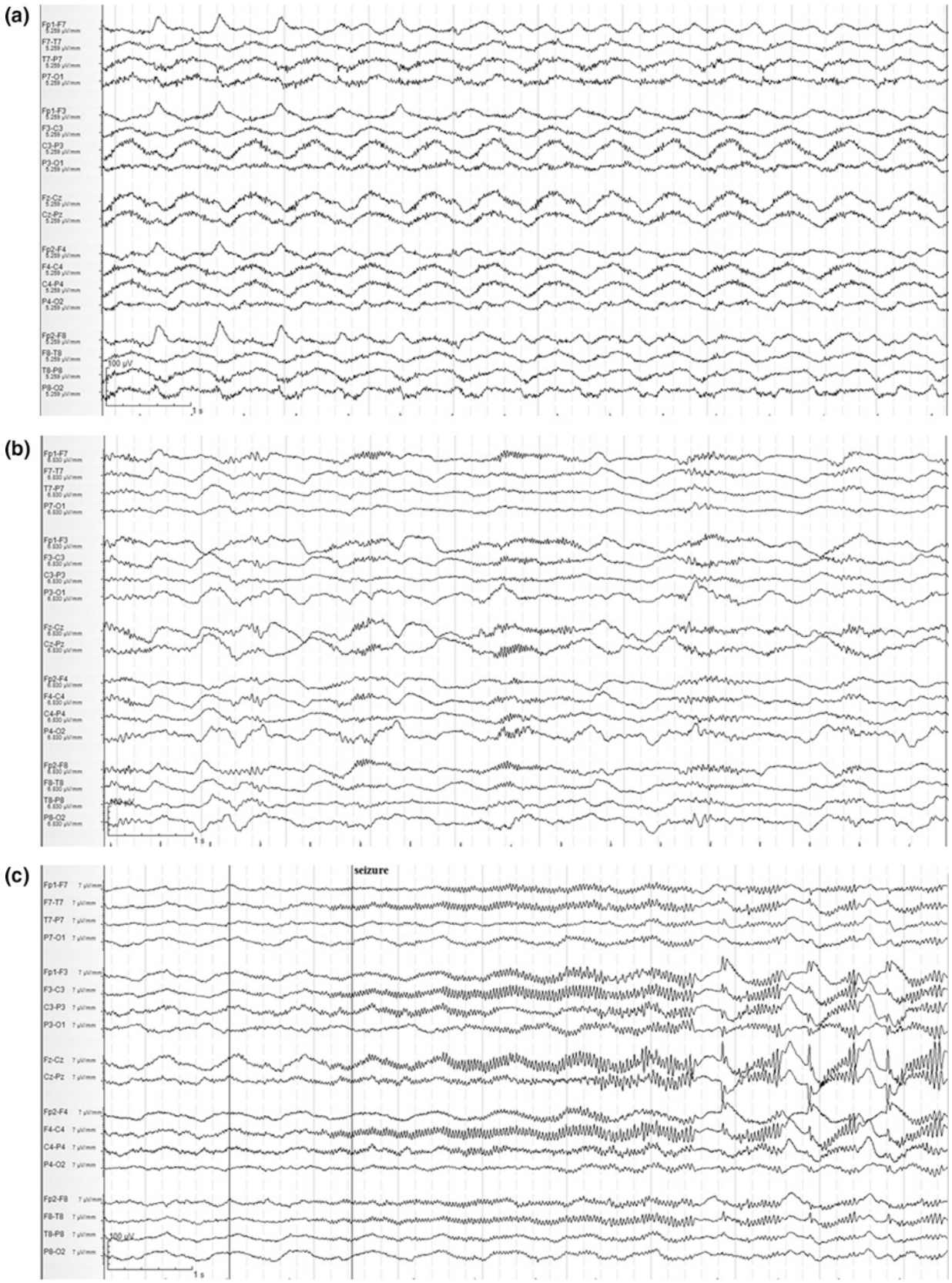
alternate between periods of akinesia and periods of violent agitation. At this stage, most patients develop typical orofacial dyskinesia, autonomic instability, and hypoventilation, often requiring prolonged ventilator support.

Electroencephalography (EEG) occupies a central place in the diagnosis of the syndrome. In most cases, it shows continuous generalized delta activity, which is often rhythmic and fluctuates in frequency. In as many as 50% of cases, the EEG shows a peculiar and disease-specific pattern of generalized rhythmic delta activity with superimposed beta or even gamma activity, termed '*extreme delta brushes*' because of their resemblance to the delta brushes of neonates [36]. Some have argued that this pattern represents SE, but this author finds it doubtful as there are no consistent clinical manifestations and response to aggressive anti-seizure treatment is often disappointing.

A few patients may also exhibit nonconvulsive status epilepticus (NCSE), with abnormal generalized paroxysmal fast activity or tonic SE during the catatonic stage (Fig. 8.1). CSF analysis is abnormal in more than 90% of cases, most commonly showing a mild lymphocytosis [34]. The antibody is not always found in the serum and should be looked for in the CSF. Brain MRI sometimes shows T2/fluid-attenuated inversion recovery (FLAIR) hyperintensities in neocortical areas or, less commonly, in the mesial temporal lobes, basal ganglia, or brainstem. Approximately half of the female patients have an ovarian teratoma. Pelvic MRI is more sensitive than CT scan and ultrasound, but the tumor can be microscopic and escape imaging techniques. Treatment includes tumor resection and immune therapy (see Chap. 17).

Encephalitis with Voltage-Gated Potassium Channel Complex Antibodies

Once thought to target the potassium channels, antibodies directed toward the voltage-gated potassium channel (VGKC) complex are now known to most frequently bind other components of a multiprotein complex that anchors the


(a)
Fp1-F7
F7-T7
T7-P7
P7-O1
Fp1-F3
F3-C3
C3-P3
P3-O1
Fz-Cz
Cz-Pz
Fp2-F4
F4-C4
C4-P4
P4-O2
Fp2-F8
F8-T8
T8-P8
P8-O2
100 µV
1 s
(b)
Fp1-F7
F7-T7
T7-P7
P7-O1
Fp1-F3
F3-C3
C3-P3
P3-O1
Fz-Cz
Cz-Pz
Fp2-F4
F4-C4
C4-P4
P4-O2
Fp2-F8
F8-T8
T8-P8
P8-O2
100 µV
1 s
(c)
seizure
Fp1-F7
F7-T7
T7-P7
P7-O1
Fp1-F3
F3-C3
C3-P3
P3-O1
Fz-Cz
Cz-Pz
Fp2-F4
F4-C4
C4-P4
P4-O2
Fp2-F8
F8-T8
T8-P8
P8-O2
100 µV
1 s

◀ **Fig. 8.1** Ten-second electroenchepalography (EEG) excerpts from continuous recording in a 19-year-old woman with anti-NMDA receptor encephalitis. During most of the recording, the EEG showed a typical pattern of extreme delta brushes, characterized by continuous rhythmic delta activity with superimposed low voltage beta activity (**a**). Occasionally, brief bursts of generalized paroxysmal fast activity occurred with little accompanying delta activity (**b**). The patient also exhibited frequent brief generalized tonic seizures. The EEG correlate was often difficult to distinguish from muscle artifact, and the patient was transiently paralyzed to better observe ictal discharges (**c**). EEG settings: low-frequency filter: 1 Hz; high-frequency filter: 70 Hz; notch filter: off

channels in the neuronal membrane, mainly the leucine-rich, glioma-inactivated 1 (LGI1), and contactin-associated protein-like 2 (Caspr2), and only rarely the channels themselves [37]. LGI1 antibodies are associated with a typical course of limbic encephalitis, while Caspr2 antibodies are more commonly associated with neuromyotonia and Morvan syndrome [37]. Low titers of antibodies can be seen in individuals with various unrelated non-autoimmune disorders and in some patients with peripheral nerve hyperexcitability, while high titers are the rule in patients with clear limbic encephalitis. This type of encephalitis is more common in men and occurs mostly after the age of 40 years. Seizures occur in 80% of cases and can be partial complex or secondary generalized seizures. Ictal autonomic manifestations, such as piloerection, have been reported. Hyponatremia (<130 mEq/l) occurs in 30–60% of cases due to the syndrome of inappropriate secretion of antidiuretic hormone (SIADH) and should raise suspicion of the diagnosis.

A peculiar type of seizure, termed faciobrachial dystonic (tonic) seizure, has been described recently in a subset of patients with anti-LGI1 encephalitis [38]. These seizures occur frequently, up to hundreds of times per day, and are characterized by brief tonic contraction of the arm and face, either on one side or, more commonly, alternating between both sides. EEG changes during faciobrachial dystonic seizures vary but most often consist of diffuse attenuation or bursts of slow waves. Faciobrachial dystonic seizures precede the manifestations of limbic encephalitis and do not respond to anti-seizure medications. In contrast, immune treatment is efficacious and might prevent the development of cognitive impairment [39]. Complex partial SE may also occur rarely [5].

CSF analysis is most often normal. Brain MRI is abnormal in 50% of cases, and commonly shows hyperintensities in the mesial temporal lobes and sometimes, basal ganglia. Most patients with anti-VGKC complex antibodies do not have an associated neoplasm, but rare paraneoplastic cases exist, mostly related to small cell lung carcinoma and thymoma. Treatment with steroids, IV immunoglobulin (IVIG), or plasma exchange is efficacious, and most patients make a full recovery. Clinical improvement usually mirrors the decrease in antibody titer in the serum.

Cases of temporal SE have also been reported in children with unspecified anti-VGKC complex antibodies [40, 41], and one case of myoclonic SE was reported in a patient with anti-Caspr2 antibodies [42].

Encephalitis with Other Antibodies Against Neuronal Surface Antigens

Several syndromes of autoimmune encephalitis with antibodies against neuronal surface antigens have been described recently. They are even rarer than the encephalitis associated with NMDA receptor and VGKC complex antibodies, but some can cause SE.

Limbic encephalitis with GABA-B Receptor, AMPA Receptor and Glycine Receptor Antibodies. Patients with antibodies against the R1 subunit of the γ-aminobutyric acid B (GABA-B) receptor present with a typical form of limbic encephalitis, with prominent seizures and complex partial SE [43–46]. The antibodies may be absent from patients' serum and detected only in the CSF. Half the cases are associated with a neoplasm, most commonly small cell lung carcinoma. Onconeural antibodies are identified in between one-third and one-half of these paraneoplastic cases, whereas non-paraneoplastic cases often present with other autoimmune diseases (including type 1 diabetes mellitus, idiopathic thrombocytopenia, and thyroiditis) or auto-antibodies (e.g., glutamic acid decarboxylase 65 [GAD65], thyroperoxidase [TPO], thyroglobulin [TG]). Most patients respond at least partially to immune treatment and tumor removal, and some make a full recovery.

Antibodies directed against the GluR 1 or GluR2 subunits of the AMPA receptor have been identified in the serum or CSF of patients with a typical course of limbic encephalitis with prominent psychiatric symptoms [46–48]. Most were middle-aged women. Similar to other antibodies against neuronal surface antigens, AMPA receptor antibodies may be absent from the patient's serum and only detectable in the CSF. Patients may have an associated neoplasm, most commonly small cell lung carcinoma. Patients responded well to treatment (immune therapy with or without tumor removal) but most had recurrent relapses, even after tumor removal.

Glycine receptor (GlyR) antibodies have been reported mainly in association with "stiff person syndrome" and progressive encephalomyelitis with rigidity and myoclonus, but a few cases of limbic encephalitis with seizures and SE have been described [49]. An association with cancer is rare.

Encephalitis and Refractory Status Epilepticus with GABA-A Receptor Antibodies. High titers of antibodies against the α1, β3, or γ2 subunits of the GABA-A receptor were identified in the serum or CSF of patients with either a typical form of limbic encephalitis or de novo refractory SE and

multifocal cortical MRI abnormalities [50, 51]. Similar to patients with GABA-B receptor antibodies, many patients had other autoimmune diseases (e.g., type 1 diabetes mellitus, idiopathic thrombocytopenia, thyroiditis, celiac disease), auto-antibodies (e.g., GAD65, TPO, TG, endomysium, VGKC complex, NMDA receptor) or both. Half of the patients who received immune therapies responded at least partially.

Encephalitis with Glutamic Acid Decarboxylase 65 Antibodies

Elevated titers of antibodies against GAD65 are found in patients with stiff person syndrome or with a specific form of cerebellar ataxia associated with type 1 diabetes mellitus. They are also present, at lower titers, in most patients with type 1 diabetes mellitus and no neurologic syndrome. GAD65 is an intracellular protein, and the pathogenic role of the auto-antibodies is debated, especially since the neurologic manifestations are so variable. Nonetheless, well-described cases of encephalitis or epilepsy associated with GAD65 antibodies have been reported [52–54]. Patients are mostly young women and exhibit a chronic course of limbic encephalitis. Both complex partial SE of temporal origin and opercular SE have been reported. Severe cases of generalized convulsive SE with autonomic instability have been described in a small group of children. These cases overlap with the syndrome associated with anti-GABA-A receptor antibodies. High serum titers of the antibody are typically found and, when tested, intrathecal synthesis is detected. Most cases are unrelated to cancer, but a few patients may have small cell lung carcinoma.

Status Epilepticus Due to Acute Disseminated Encephalomyelitis and Multiple Sclerosis

Patients with multiple sclerosis are at higher risk of seizures compared to the general age-matched population, possibly because of cortical demyelination and inflammation [55, 56]. Focal SE is possible but rare [57–59].

Seizures are more frequent with acute disseminated encephalomyelitis (ADEM), especially in severe cases, where they can occur in up to two-thirds of patients [60, 61]. *Epilepsia partialis continua* and NCSE are infrequent but possible manifestations [62].

Steroid-Responsive Encephalopathy with Autoimmune Thyroiditis

Steroid-responsive encephalopathy with autoimmune thyroiditis (SREAT), previously called Hashimoto encephalopathy, manifests by various combinations of subacute encephalopathy (e.g., rapid-onset dementia, delirium, alteration of consciousness), movement disorders (e.g., myoclonus, ataxia, tremor), and stroke-like episodes [63]. Seizures occur in up to two-thirds of cases. Some patients have hypothyroidism or hyperthyroidism, and all show high serum titers of antibodies directed against thyroperoxydase (TPO) or thyroglobulin (TG). The patient's response to steroids is usually striking. A few cases of isolated generalized convulsive SE or NCSE in association with high titers of thyroid antibodies have been reported [5, 64, 65]. Whether they represent a subtype of SREAT or a separate entity is unclear, especially since antibodies against neuronal surface antigens can be found in some patients with thyroid antibodies [50].

Status Epilepticus Due Secondary to a Systemic Inflammatory Disorder

The mechanisms by which systemic inflammation can lead to seizures and SE are multiple and overall poorly understood.

Seizures happen in approximately 15% of cases of SLE and are part of the primary diagnostic criteria [66]. Seizures often occur at SLE onset and tend to accompany disease flares. Generalized convulsive SE, NCSE, and complex partial SE have all been reported [67, 68]. Patients with anti-phospholipid antibodies and strokes are at higher risk, but cerebral ischemia is not the only cause of seizures [69]. Some patients with antinuclear antibodies also exhibit antibodies against neuronal surface antigens. The posterior reversible encephalopathy syndrome (PRES; see below), which frequently causes seizures and SE, is increasingly recognized as a complication of SLE and other systemic autoimmune diseases [70]. Other systemic inflammatory disorders that have been associated with SE are listed in Table 8.2.

Uncommon Infections

Seizures frequently complicate infections of the central nervous system [71], and SE is independently associated with worse outcome in this setting [19]. While encephalitis is often listed as a cause of SE, an infectious agent is identified in only a quarter to a third of cases [18–20, 72]. Type 1 Herpes Simplex, Varicella Zoster, and Enteroviruses are the most frequently identified pathogens. Aside from them, there is a dauntingly long list of uncommon viruses, bacteria, parasites, and fungi that can cause encephalitis and SE (Table 8.3). Not all pathogens that cause encephalitis have been linked to SE, but this is likely due in part to the

Table 8.3 Uncommon infectious causes of status epilepticus

Categories	Pathogens
Atypical bacteria	*Bartonella hanselae*
	Treponema pallidum
	Coxiella burnetii
	Mycoplasma pneumoniae
	Orientia tsutsugamushi (Scrub typhus)
	Shigella sp.
	Chlamydia psittaci
	Ehrlichia chaffeensis/Anaplasma phagocytophilum
	Rickettsia spp.
	Leptospira spp.
Viruses	Herpes viruses *Cytomegalovirus* *Epstein–Barr virus* *Human Herpes Virus-6*
	Arboviruses *Flaviviruses (Tick-borne complex/Japanese, West Nile, Saint-Louis, Murray Valley)* *Bunyaviruses (California, La Crosse, Toscana, Jamestown Canyon, Rift Valley Fever)* *Togaviruses (Eastern Equine, Western Equine)* *Reoviruses (Colorado Tick Fever)*
	Influenza A Influenza B Parvovirus B19 HIV Measles Rubella Mumps (parotitis) Hendra virus Polyoma viruses
Parasites	Paragonimiasis
	Cysticercosis
	Plasmodium falciparum
	Toxoplasma gondii
	Acanthamoeba spp.
	Balamuthia mandrillaris
	Baylisascaris procyonis
Fungi	Paracoccidioidomycosis
	Mucormycosis
	Absidiomycosis
	Cryptococcus sp.
	Histoplasma sp.

Note Only pathogens for which an association with status epilepticus was clearly described are presented in this table. It is possible that encephalitis caused by pathogens other than those listed above can lead to SE

limited description of seizures in most case series and the uneven use of continuous of EEG monitoring. The list of infections presented here should not be considered exhaustive, and a complete work-up is advised when an encephalitis is suspected. An approach consisting of the blind ordering of random tests should be discouraged. Rather, a diagnostic algorithm tailored to each patient and based on host and environmental factors, clinical presentation, and results from initial blood and CSF analysis and brain MRI, is recommended [73, 74] (Table 8.4).

Table 8.4 Clues to the etiology of status epilepticus

Clues	Etiology
Immune treatment and status	
Immunocompromised (AIDS, immunosuppressive drugs)	Cytomegalovirus, Human Herpes Virus-6, Varicella Zoster Virus, Human Immunodeficiency Virus, West Nile Virus, *Mycoplasma tuberculosis*, *Cryptococcus neoformans*, *Histoplasma capsulatum*, *Toxoplasma gondii*
Immunosuppressive and chemotherapeutic agents	PRES and direct drug toxicity
Substance abuse	
Alcohol	Withdrawal, Subacute encephalopathy with seizures in alcoholism
Injected drugs	Direct toxicity; also AIDS and related infections
Ingestion	
Unpasteurized milk	Tick-borne virus, *Coxiella burnetii*
Star fruit	Caramboxin, oxalic acid
Occupational exposure to toxic substances	Toxin-related
Geographical factors (residence, recent travel)	
Africa	West Nile virus
Australia	Murray Valley encephalitis virus, Japanese encephalitis virus, Hendra virus
Central and South America	Eastern Equine Virus, Western Equine Virus, Venezuelan Equine Virus, Saint-Louis Virus, Rickettsia spp.
Europe	West Nile Virus, Tick-borne Virus, *Ehrlichia chaffeensis/Anaplasma phagocytophilum*
India, Nepal	Japanese Virus
Middle East	West Nile Virus
Russia	Tick-borne Virus
Southeast Asia, China, Pacific Rim	Japanese Virus, Tick-borne Virus, Nipah Virus
Seasonal factors	
Late summer/early fall	Arboviruses, Enteroviruses
Winter	Influenza Virus
Animal exposure	
Cats	Bartonella henselae, *Toxoplasma gondii*
Horses	Eastern Equine Virus, Western Equine Virus, Venezuelan Equine Virus, Hendra Virus
Raccoons	*Baylisascaris procyonis*
Rodents	*Bartonella quintana*, Eastern Equine Virus, Western Equine Virus, Tick-borne Virus, Powassan Virus, La Crosse Virus
Sheeps and goats	*Coxiella burnetii*
Swine	Japanese Virus, Nipah Virus
Insect exposure, including travel to infested area	
Mosquitoes	Eastern Equine Virus, Western Equine Virus, Venezuelan Equine Virus, Saint-Louis Virus, Murray Valley Virus, Japanese Virus, West Nile Virus, La Crosse Virus
Ticks	Tick-borne Virus, Powassan Virus, Rickettsia spp., *Ehrlichia chaffeensis/Anaplasma phagocytophilum*
Prodromal symptoms	
Prominent behavioral and psychiatric features	Anti-NMDA receptor encephalitis
Prominent memory issues	Limbic encephalitis, anti-VGKC complex encephalitis
Respiratory symptoms	NORSE/FIRES, ADEM, *Mycoplasma pneumoniae*
Gastrointestinal symptoms	NORSE/FIRES, ADEM

(continued)

Table 8.4 (continued)

Clues	Etiology
General examination	
Fever	Infectious or inflammatory encephalitis
Rash	Cytomegalovirus, Varicella Zoster Virus, Human Herpes Virus-6, West Nile Virus, Enterovirus, *Rickettsia rickettsii*, *Mycoplasma pneumoniae*, *Ehrlichia chaffeensis*/*Anaplasma phagocytophilum*
Excoriating skin lesion	Bartonella spp.
Regional adenopathy	Bartonella spp., *Mycoplasma tuberculosis*
Generalized adenopathy	Human Immunodeficiency Virus, Epstein–Barr Virus, Cytomegalovirus, West Nile Virus, *Treponema pallidum*, *Toxoplasma gondii*
Retinitis	Cytomegalovirus, West Nile Virus, *Bartonella henselae*
Parotitis	Mumps
Hepatitis	*Coxiella burnetii*
Respiratory tract findings	Cytomegalovirus, Venezuelan Equine Virus, Nipah Virus, Hendra Virus, Influenza, Adenovirus, *Mycoplasma pneumoniae*, *Coxiella burnetii*, *Mycoplasma tuberculosis*, *Histoplasma capsulatum*
Neurologic examination	
Acute lower motor neuron syndrome	Japanese Virus, West Nile Virus, Tick-borne Virus, Enterovirus (serotype 71, Coxsackie)
Acute parkinsonism	Japanese Virus, Saint-Louis Virus, West Nile Virus, Nipah Virus, *Toxoplasma gondii*
Prominent oro-lingual dyskinesias	Anti-NMDA receptor encephalitis
Faciobrachial dystonic seizures	Anti-VGKC complex (LGI1) encephalitis
Ataxia	Epstein–Barr Virus, mitochondrial disorder
EEG	
Extreme delta brushes	Anti-NMDA receptor encephalitis
Extreme spindles	Mycoplasma pneumoniae
Parieto-occipital epileptiform discharges and seizures	Mitochondrial disorder, PRES
MRI	
Prominent mesial temporal lobe involvement	Paraneoplastic and autoimmune limbic encephalitis, anti-VGKC complex encephalitis
Basal ganglia	Saint-Louis Encephalitis Virus, La Crosse Virus, and Murray Valley Virus
PRES images	PRES
Stroke-like images	POLG1, MELAS
CSF	
Normal protein levels and cell count	Genetic disorder
Elevated lactate	Mitochondrial disorder
Eosinophils	Parasitic encephalitis
Blood and serum	
Elevated liver tests	Mitochondrial disorder (esp. POLG1), Rickettsia spp., Cytomegalovirus

Abbreviations: *PRES* posterior reversible encephalopathy syndrome; *AIDS* acquired immunodeficiency syndrome; *NORSE* new-onset refractory status epilepticus; *FIRES* febrile illness-related epilepsy syndrome; *ADEM* acute disseminated encephalomyelitis; *spp.* species; *POLG1* polymerase gamma 1; *MELAS* myopathy, encephalopathy, lactic acidosis, and stroke; *NMDA* N-methyl-D-aspartate; *VGKC* voltage-gated potassium channel; *LGI1* leucine-rich, glioma inactivated 1; *CSF* cerebrospinal fluid

Atypical Bacteria

Cat-Scratch Disease. Bartonella henselae (or rarely, Bartonella quintana) causes cat-scratch disease, also known as regional lymphadenitis. It occurs mostly in children and presents as regional lymphadenopathy near the site of the inoculating bite or scratch from a cat. An excoriated macular or papular skin lesion can often be seen at the site of inoculation. Most patients also present with systemic symptoms, such as fever, fatigue, and myalgia. In 1–2% cases, a severe meningoencephalitis ensues and is often complicated by generalized convulsive SE [75–78]. Treatment includes anti-seizure medications and antibiotics (azithromycin and rifampin in children, or doxycycline and rifampin in adults).

Mycoplasma Pneumonia. A severe form of encephalitis causing refractory SE has been reported in association with *Mycoplasma pneumoniae* [5, 79, 80]. Most cases occurred in children and young adults and were preceded by a febrile upper respiratory illness. The diagnosis relied mostly on serology, while direct identification of the pathogen in the CSF by culture or PCR was often not reported or negative, suggesting that a large number of cases might result from a postinfectious immune process. A peculiar EEG pattern of transient extreme spindles has been reported in a two children with *M. pneumoniae* encephalitis [81, 82].

Uncommon Viruses

Cytomegalovirus. Cytomegalovirus (CMV) encephalomyelitis preferentially occurs in immunocompromised patients, especially those with AIDS or receiving immunosuppressive drugs after transplant, and is often due to reactivation of latent virus in individuals with a low CD4 cell count (<50 cells/μl). Involvement of the nervous system by CMV in immunocompetent patients is rare but well documented and constitutes the second most frequent manifestations of infection after gastrointestinal illness [83, 84]. Patients present with a combination of symptoms and signs of myelitis, encephalitis, meningitis, or radiculopathy. Extra-CNS involvement is frequent and includes hepatitis, colitis, pneumonitis and retinitis. CSF abnormalities are nonspecific and variable. Pleocytosis is usually absent or mild and consists predominantly of lymphocytes and monocytes. Elevated protein levels are also rare. Brain MRI may be normal but sometimes shows diffuse or patchy T2/FLAIR hyperintensities in the white matter; images of ventriculitis can also be seen and should suggest the diagnosis [85].

Epstein–Barr Virus. Neurologic complications of EBV infection are uncommon. In immunocompromised patients, it is typically associated with primary lymphoma of the CNS, while in immunocompetent patients it has been associated with a variety of neurologic manifestations, including cerebellitis, ADEM, encephalomyeloradiculitis, Guillain–Barré syndrome, and Bell's palsy. Contrary to the case in HSV1 and CMV infections, the likely mechanism of EBV-associated neurologic complications is a postinfectious immune process. Encephalitis with seizures can occur with an initial EBV infection in children and young adults, usually in the absence of symptoms of infectious mononucleosis [86]. Isolated refractory SE has also been reported.

Human Herpes Virus-6. Acute Human Herpes Virus-6 (HHV-6) infection causes roseola in children and is associated with febrile seizures [87]. The virus is known to integrate in human DNA and can be detected in body tissues and fluids throughout the lifetime, including in asymptomatic individuals. It has been detected in a high proportion of surgical specimen of mesial temporal sclerosis [88].

HHV-6 reactivation after allogeneic hematopoietic stem cell transplantation is associated with a distinct syndrome of fever, rash and acute limbic encephalitis (referred to as post-transplant acute limbic encephalitis, or PALE) [89]. The incidence is higher after umbilical cord blood transplantation. As with noninfectious limbic encephalitis, temporal lobe seizures are frequent and can evolve to SE.

Arboviruses. Arboviral infections are an increasingly important cause of encephalitis worldwide, due to both the emergence of new strains and the expansion of known pathogens [90]. Fever, headache, malaise, myalgia, vomiting, and nausea precede the neurologic manifestation and occur within days after inoculation. A variety of symptoms and signs of meningoencephalomyelitis can occur. Seizures, sometimes evolving to SE, are common to almost all arbovirus encephalitides. Parkinsonism is common in Dengue, Japanese Virus, West Nile Virus, Eastern Equine Virus, and Western Equine Virus encephalitides. An acute lower motor neuron syndrome is frequent with Dengue, Japanese Virus, West Nile Virus, and Tick-borne Virus infections. Laboratory and imaging findings can be nonspecific or normal, particularly in the early stages of disease. CSF findings include lymphocytic pleocytosis with mild protein elevation. CSF glucose is usually normal, but low glucose levels can be seen. Rapid serum or CSF antibody assays are available for most of the arboviruses. Brain MR imaging may be normal in early or mild cases. Certain viruses have a predilection for certain areas of the brain. Japanese Virus can affect basal ganglia, brainstem, or spinal cord. The basal ganglia may also be involved in Saint-Louis, La Crosse, and Murray Valley encephalitides. A variety of nonspecific EEG abnormalities can be seen. Triphasic waves have been reported in West Nile Virus encephalitis.

Other uncommon infectious causes of SE, including parasites and fungi, are summarized in Table 8.3.

Genetic and Congenital Causes of Status Epilepticus

Epilepsy is a common trait of numerous genetic and congenital neurologic disorders (Table 8.5). A recent systematic review identified more than 120 genes whose mutations were associated with status epilepticus [91]. The vast majority of these mutations cause rare syndromes that are encountered primarily in neonates, infants, and children. Seizures and SE are only a part of a syndrome that also comprises other signs, such as dysmorphic features, cutaneous abnormalities, failure to thrive, organ failure, cerebral malformations, etc. Most of these disorders can be subdivided into those associated with inborn errors of metabolism, including mitochondrial disorders, malformations of cortical development, neurocutaneous syndromes, and epileptic encephalopathies. Seizures are often a nonspecific manifestation, and the diagnosis will often be known or suspected by the time SE occurs. Discussed below are the main examples in which SE might be the initial or only manifestation of a genetic disorder or in which its characteristics are so specific that they lead to the diagnosis.

Mitochondrial Disorders

Epilepsy occurs in 20–50% individuals with mitochondrial disease and is often an early manifestation [92]. Prevalence varies and is highest with the m.8344A>G point mutation (>90%), often as part of MERFF (mitochondrial encephalopathy with ragged-red fibers) syndrome, the m.3243A>G mutation (35%), polymerase gamma 1 (POLG1) mutations (25%), and the less common m.12147G>A, m.8993T>G, and recessive TRIT1 mutations. Other mutations, including large mitochondrial DNA deletions, are much less likely to cause epilepsy, with reported rates <10%. These differences in epilepsy risk are poorly understood and are possibly related to the preferential involvement of cortical interneurons [93] or the occurrence of focal energy failure, as in stroke-like episodes.

A wide range of seizure phenotypes can occur, and individual patients can present with several distinct seizure types. While patients with the m.8344A>G almost always exhibit myoclonic seizures (but rarely SE), the commonest seizure manifestation in other genotypes is focal seizures with or without secondary generalization [92].

Status epilepticus has been reported in patients with m.3243A>G and m.12147A>G mutations. In all cases, this was in the setting of mitochondrial encephalopathy with lactic acidosis and stroke-like episodes syndrome (MELAS) [94]. Affected patients are mostly children and young adults, but onset in later adulthood is increasingly recognized [95–98]. The A467T and W748S mutations in the POLG1 gene cause juvenile or early adult-onset Alpers-Huttenlocher hepatocerebral syndrome [99–101]. Occipital epilepsy is the presenting symptom in most cases and often occurs together with or soon after the onset of migraine-like headaches [102, 103]. Patients develop focal motor seizures with secondary generalization, myoclonic seizures, and *epilepsia partialis continua*. Nystagmus, ataxia, neuropathy, and external ophthalmoplegia are inconstant features. Stroke-like episodes can also occur. Liver involvement is variable but can lead to fulminant liver failure and necrosis and is sometimes precipitated by the use of valproate. Lactic acid is sometimes, but not always, elevated in the CSF.

Treatment of SE in the setting of mitochondrial disorder is supportive. Potential precipitants, including infection, dehydration, and metabolic derangements, should be identified and treated. Comorbidities (cardiomyopathy, ileus) should be considered, particularly in the critically ill patient. Valproate should be avoided, especially in patients who might carry POLG mutations, due to potential fulminant hepatoxicity. Oral L-arginine supplementation lessens the severity and frequency of stroke-like episodes in MELAS [104–106]. It thus might also prove useful to control SE in this setting, given the tight association between these two complications.

Ring Chromosome 20 Syndrome

Ring chromosome 20 syndrome is a rare chromosomal abnormality, where the two arms of chromosome 20 fuse to form a ring chromosome [107]. It is associated with seizures and mental retardation. The q13.33 region of chromosome 20, which is involved in the fusion, includes two genes that are related to other epilepsy syndromes: nicotinic acetylcholine receptor alpha-4 subunit, associated with autosomal dominant nocturnal frontal lobe epilepsy, and the potassium voltage-gated potassium channel KQT subfamily member 2, associated with benign familial neonatal convulsions [108]. It is possible that microdeletions in this region of the ringed chromosome may cause epilepsy in affected patients.

Epilepsy does not affect all individuals with this syndrome but is the most consistent feature [107, 109]. Seizures often begin in childhood. Multiple seizure types usually happen in the same individual. They include partial complex seizures, often arising from the frontal lobe, tonic seizures, and generalized tonic-clonic seizures. Frontal lobe seizures can occur during the night, with subtle manifestations such as stretching and turning that resemble arousal or terror and hallucinations, and may be misdiagnosed as nightmares or another sleep disorder.

Perhaps the most characteristic seizure type in the syndrome is prolonged episodes of NCSE, resembling atypical absence SE, during which the children are confused and

Table 8.5 Genetic and congenital disorders causing status epilepticus

Chromosomal abnormalities	Angelman syndrome
	Wolf–Hirschhorn syndrome
	Ring chromosome 20, 17, 14
	Fragile X syndrome
	X-linked mental retardation syndromes
Inborn errors of metabolism	Disorders of amino acid metabolism *D-and L-2-hydroxyglutaric aciduria* *D-glyceric academia* *Lysinuric protein intolerance* *Maple syrup urine disease* *Phosphoserine aminotransferase deficiency* *3-phosphoglycerate dehydrogenase deficiency* ***3-Methylcrotonyl-CoA carboxylase deficiency*** *Hyperprolinemia*
	Disorder of citric acid metabolism (Krebs cycle) *Fumaric aciduria*
	Disorder of copper metabolism *Wilson disease* *Menkes disease*
	Disorder of creatine metabolism *Guanidinoacetate methyltransferase deficiency*
	Disorder of cytosolic protein synthesis *Cytosolic glutaminyl-tRNA synthetase*
	Disorder of fatty acid metabolism *Combined oxidative phosphorylation deficiency* *Carnitine palmitoyl-transferase II deficiency* *3-hydroxyacyl-CoA dehydrogenase deficiency*
	Disorder of cerebral folate transport *Folate transporter deficiency*
	Disorder of GABA metabolism *GABA transaminase deficiency* *Succinic semialdehyde dehydrogenase deficiency*
	Disorders of glycine metabolism *Glycine encephalopathy/nonketotic hyperglycinemia*
	Disorder of glucose transport *Glucose transporter 1 deficiency*
	Disorder of glycosylation *Asparagine-linked glycosylation defect*
	Disorders of lipid storage *Gaucher disease type 3* *GM2 gangliosidosis (Tay–Sachs)* *GM2 gangliosidosis (Sandhoff)* *Metachromatic leukodystrophy* *Adrenoleukodystrophy* Peroxisomal biogenesis disorders *Zellweger syndrome* *Refsum syndrome*
	Disorders of purine and pyrimidine metabolism *Adenylosuccinase deficiency* *Beta-ureidopropionase deficiency* Vitamin-responsive disorders ***Pyridoxine-dependent epilepsy*** ***Pyridoxal-5′-phosphate-dependent epilepsy*** ***Folinic acid-dependent epilepsy*** **Cobalamin C/D deficiency** ***Biotinidase deficiency/Multiple carboxylase deficiency***

(continued)

Table 8.5 (continued)

	Urea cycle defects *Ornithine transcarbamylase deficiency* *Citrullinemia type 11*
	Disorders of heme metabolism ***Acute porphyrias***
	Others *Aicardi–Goutières syndrome 6* *Alexander disease* *GM3 synthase deficiency* *Molybdenum cofactor deficiency* *Mucopolysaccharidosis type II (Hunter syndrome)* *1-Phosphatidylinositol-4,5-bisphosphate phosphodiesterase beta-1 defects* *Nonketotic hyperglycinemia* Pyruvate carboxylase deficiency
Progressive myoclonic epilepsies	Unverricht–Lundborg disease
	Lafora disease
	Progressive myoclonic epilepsy type 3–7
	Myoclonus epilepsy and ragged-red fibers (MERRF)
	Sialidosis—type 1
	Sialidosis—type 2
	Neuronal ceroid lipofuscinoses 2 (Jansky–Bielschowsky disease)
	Neuronal ceroid lipofuscinoses 3
	Neuronal ceroid lipofuscinoses 6 (Kufs' disease)
Early childhood epileptic encephalopathies and severe epilepsy syndromes of infancy and childhood	**Dravet syndrome (severe myoclonic epilepsy in infancy)**
	Lennox–Gastaut syndrome
	Malignant epilepsy with migrating partial seizures in infancy
	Early infantile epileptic encephalopathy (Ohtahara syndrome)
	West syndrome (Infantile spasms)
Benign focal epilepsies of childhood	Panayiotopoulos syndrome
Idiopathic generalized epilepsy syndromes	**Epilepsy with phantom absences**
Malformations of cortical development	**Focal cortical dysplasia**
	Schizencephaly
	Heterotopias
	Polymicrogyria
	Hemimegalancephaly
	Lissencephaly
Neurocutaneous syndromes	Sturge–Weber syndrome
	Tuberous sclerosis
	Hypomelanosis of Ito
	Neurocutaneous melanomatosis
Mitochondrial disorders	**Alpers-Huttenlocher/POLG1 syndrome**
	MELAS
	MERFF
	IOSCA

(continued)

Table 8.5 (continued)

Others	**CADASIL**
	Wolfram syndrome
	Rett syndrome
	PMSE syndrome
	Robinow syndrome
	Kabuki syndrome
	Cockayne syndrome
	Wrinkly skin syndrome
	Familial encephalopathy with neuroserpin inclusion bodies

Note Syndromes in which SE is a prominent or can be an isolated feature are indicated in bold. Abbreviations: *GABA* gamma- aminobutyric acid; *POLG1* polymerase gamma 1; *MELAS* myopathy, encephalopathy, lactic acidosis, and stroke; *MERRF* myoclonic epilepsy with ragged-red fibers; *IOSCA* infantile-onset spinocerebellar ataxia; *CADASIL* cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy

have decreased awareness, are staring, and sometimes appear frightened [107, 110, 111]. These episodes may be hard to recognize and can last for hours or even days. They may end with a tonic-clonic seizure. Ictal EEG shows a specific pattern of generalized waxing and waning rhythmic irregular spike-and-wave complexes or high-amplitude slow waves at 2-4 Hz with a frontal predominance. Between seizures, the EEG can show generalized spike-and-wave discharges or rhythmic theta activity with a frontal predominance [109, 112].

Most affected children also have some degree of intellectual disability and behavioral difficulties. Although these issues can appear either before or after the onset of epilepsy, they tend to worsen after seizures develop [113]. Unlike most other chromosomal disorders, congenital malformations and dysmorphism are rarely seen, but slow growth, short stature, microcephaly, and subtle abnormalities of facial features can occur.

The ring 20 abnormality is not present in all cells of affected individuals and may be limited to as few as 5% of cells [108]. Comparative genomic hybridization (CGH) array will not detect the ring chromosome and karyotype analysis examining at least 50 cells should be requested to screen properly for chromosomal mosaicism. Treatment is symptomatic, but seizures are often refractory.

Late-Onset Neuronal Ceroid Lipofuscinoses

Neuronal ceroid lipofuscinoses are a family of neurodegenerative lysosomal storage disorders characterized by progressive cognitive decline, epilepsy, ataxia, and visual loss resulting from the intracellular accumulation of lipofuscin in tissues, including in the cortex and in the retina [114]. At least 10 different variants have been described and classified according to their age of onset (infantile, late infantile, juvenile, and adult) and several causative genes identified. Epilepsy manifests by cortical myoclonus and generalized tonic-clonic seizures. Status epilepticus is infrequent and usually occurs in the setting of the full-blown syndrome but rare cases of late-onset ceroid lipofuscinoses (Kufs' disease) can present initially as isolated *epilepsia partialis continua* [115]. The diagnosis is made by electronic microscopy studies of skin biopsy (although they can be negative in adult-onset cases) and confirmed by genetic testing. Treatment is supportive.

Porphyria

The porphyrias are a family of genetic metabolic disorders caused by deficiencies in the heme biosynthetic pathway [116]. They can be subdivided into acute and non-acute porphyrias on the basis of their major clinical manifestations. The acute porphyrias are characterized by acute life-threatening attacks of abdominal pain and neurologic symptoms such as peripheral neuropathy and mental disturbance. Acute attacks are precipitated by a variety of factors, including drugs, alcohol, infections, surgery, pregnancy, and reduced caloric intake. Seizures occur in approximately 10–20% of attacks. The most common types of seizures are complex partial or tonic-clonic seizures. Status epilepticus is rare but has been reported in a few well-described instances [117, 118]. All were adult patients, and SE was part of the initial presentation for all subjects. Convulsive, nonconvulsive, and complex partial SE and *epilepsia partialis continua* have been reported [119–121]. The pathogenesis of seizures and SE in acute porphyria attacks is unclear. A direct neurotoxic effect of aminolevulinic acid has been posited, but some cases of

porphyria-related SE have shown reversible T2/FLAIR abnormalities similar to those seen in PRES, another known complication of acute porphyria [122–124]. Diagnosis is made by demonstrating increased urinary excretion of porphobilinogen during the attack and confirmed by genetic testing. Treatment is symptomatic; it can be challenging, as most anti-seizure medications (including valproate, phenobarbital, phenytoin, primidone, carbamazepine, clonazepam, ethosuximide, lamotrigine, felbamate, tiagabine, and topiramate) may exacerbate attacks of acute porphyria. Levetiracetam, gabapentin, and propofol appear to be safe options [125, 126].

Other Inborn Errors of Metabolism

Other inborn errors of metabolism that can present with prominent or isolated SE in neonates and infants include biotinidase deficiency [127], folinic acid-dependent epilepsy, pyridoxine-dependent epilepsy [128], pyridoxal 5′ phosphate-dependent epilepsy [129], cobalamin C/D deficiency [130], and 3-methylcrotonyl-CoA carboxylase deficiency [131]. Their recognition is important because children often benefit, at least partly, from vitamin supplementation and adapted diet.

Malformations of Cortical Development

Malformations of cortical development, including focal cortical dysplasia and schizencephaly, are a common cause of refractory epilepsy. Occasionally, they can manifest abruptly as a seizure cluster or SE [132–136]. In one study, they represented the third most common cause of new-onset SE in children [137]. Several cases of SE have also been reported following incomplete resection of cortical dysplasia [138, 139].

Drug-Induced Status Epilepticus

Drug-induced SE accounts for less than 5% of SE although there seems to be an endless list of drugs suspected of causing seizures and SE, either at therapeutic doses or due to accidental or intentional overdose (Table 8.6). A causal relationship is difficult to establish for most incriminated substances, as several confounders (e.g., prior epilepsy or other neurologic disorder, concomitant organ failure, or electrolyte imbalance) are often present, and the available information originates mostly from case reports or small uncontrolled case series. The subject has been reviewed and discussed recently [140].

Anti-seizure Medications

It might appear paradoxical that drugs aimed at preventing seizures may cause seizures and even SE. Further, the occurrence of SE in patients treated for epilepsy could be easily attributed to the underlying disorder rather than to its treatment. There is enough evidence, however, to indicate that anti-seizure medications may occasionally cause SE. This is especially the case for sodium-channel blocking (mostly phenytoin, carbamazepine [141], oxcarbazepine [142, 143] and lamotrigine [141]) and GABA-ergic (tiagabine [141] and vigabatrin [144]) drugs mistakenly prescribed to patients with idiopathic generalized epilepsy, in which they are known to precipitate absence SE or myoclonic SE. Now seldom prescribed, tiagabine can precipitate episodes of SE, both in patients with epilepsy and in individuals with no prior history of epilepsy [145–149]. Tiagabine-induced SE presents as altered consciousness with myoclonia. The EEG shows prolonged runs of sharp-and-slow wave, spike-and-wave or polyspike-and-wave discharges. The mechanism is unclear and possibly includes tonic inhibition of cortical interneurons and enhancement of thalamo-cortical oscillatory networks. Management includes discontinuation of tiagabine, administration of benzodiazepines, and if necessary, substitution of another anti-seizure medication. A similar syndrome has been reported rarely with pregabalin in elderly individuals with chronic renal failure [145], and possibly also with valproate.

Antibiotics

Cephalosporins exert a neurotoxic and proconvulsant effect by inhibiting GABA-A receptor-mediated chloride currents and cause encephalopathy, myoclonus, seizures, and NCSE [150–156]. Many, but not all, affected patients are elderly or critically ill individuals with impaired renal function. The EEG shows generalized periodic or spike-and-wave discharges. When toxicity occurs, withdrawal of the offending antibiotic is necessary. Hemodialysis or hemofiltration can remove the circulating drugs quickly and may be sufficient. If SE does not improve, short-term anti-seizure treatment may be required.

Seizures and confusion, but very rarely SE, may occur in patients taking fluoroquinolones [157] and anti-malarial drugs (chloroquine) [158] possibly through a similar GABA-A antagonistic effect.

Isoniazid can cause SE by depleting pyridoxine, which is a cofactor of glutamic acid decarboxylase, the rate-limiting enzyme in GABA synthesis [159]. Most cases are due to accidental ingestion of the drug by children. Pyridoxine replacement therapy is efficacious.

Table 8.6 Status epilepticus caused by drugs, toxins, or related to medical intervention

Drugs	
Anti-seizure drugs	Tiagabine
	Vigabatrin
	Sodium-channel blockers (carbamazepine, phenytoin, lamotrigine, etc.)
	Pregabalin
	Valproate
Antibiotics	Cephalosporins
	Carbipenem
	Isoniazid
	Quinolones
	Mefloquine, chloroquine
Antidepressants	Bupropion
	Tricyclic antidepressants, especially amoxapine
	Selective serotonin reuptake inhibitors
	Lithium
Antipsychotic	Neuroleptic malignant syndrome
Chemotherapy	Combinational chemotherapy
	Platinum-based agents
	Cytarabine
	Gemcitabine
	Irinotecan
	Interferon-alpha
	Interleukin-2
	Humanized monoclonal antibodies
	Bevacizumab
	Ipilimumab
	Rituximab
	Infliximab
	Tyrosine kinase inhibitors
	Imatinib
	Pazopanib
	Sorafenib
	Sunitinib
	GMCSF
	Ifosfamide
Immunosuppressive and immunomodulatory drugs	Cyclosporine
	Tacrolimus
	Sirolimus
	Intravenous immune globulines
	Anti-TNF-alpha (etanercept)
	Anti-lymphocyte globulin
	High-dose steroids
Other medications	Lindane
	Permethrin
	Flumazenil

(continued)

Table 8.6 (continued)

Drugs	
	4-aminopyridine (dalfampridine)
	Sulfasalazine
	Theophylline
	Anti-histamines
	Opiates (morphine, tramadol)
Complementary and alternative medicines	Borage oil
	Neem oil
Recreational drugs	Alcohol and SESA
	Cocaine
	Amphetamines
	Ecstasy
	Lysergic amine acid
	Synthetic cannabinoids ("spice")
	Glue and petrol sniffing
Environmental toxins	Lead
	Aluminum
	Star fruit (oxalic acid, caramboxin)
	Organophosphates, organochlorines and pyrethroids
	Biotoxins (scorpion toxin, anatoxin, ciguatoxin, domoic acid)
	Cyanide
Medical interventions	Radiotherapy (*SMART syndrome)* Electroconvulsive therapy Epilepsy surgery: *Implantation of intracranial electrodes* *Temporal lobectomy* *Partial resection of focal cortical dysplasia*
	Carotid revascularization (angioplasty/stenting/endarterectomy): *Cerebral hyperperfusion syndrome*
	Contrast medium-enhanced CT/angiography/cerebral angiography

Abbreviations: *TNF* tumor-necrosis factor; *SMART* stroke-like migraine attacks after radiation therapy; *SESA* subacute encephalopathy with seizures in chronic alcoholism

Chemotherapy and Immunotherapy

Seizures and SE are a rare complication of many chemotherapy and immunotherapy agents. In most instances, they develop in the context of PRES.

In contrast, ifosfamide toxicity has both a different mechanism and clinical presentation. It manifests with progressive encephalopathy with confusion, delirium, and myoclonus [160]. Electroencephalographic abnormalities are present in up to two-third of cases, some with a clear NCSE electroclinical picture, including response to i.v. benzodiazepines. Brain MRI is most often normal. Suggested mechanisms of toxicity include disruption of fatty acid oxidation in the liver and a direct neurotoxic effect of chloroacetaldehyde, its main metabolite. In addition to cessation of drug administration, treatment with methylene blue is effective and can quickly reverse the encephalopathy. Its effect is transient, and repeated administration every 4 h is required.

Toxin-Related Status Epilepticus

Alcohol and Subacute Encephalopathy with Seizures in Chronic Alcoholism (SESA)

Alcohol is probably the toxic substance most frequently associated with seizures and SE, often in the context of withdrawal in chronic abusers or in the aftermath of a period of binge drinking [1–3]. Seizures usually occur within 48 h after the last drink and evolve to SE in 20–40% of cases. Given the high prevalence of chronic alcohol abuse,

alcohol-withdrawal SE may account for up to 10–15% of all SE cases. SE is almost always of the general convulsive type and often responds well to benzodiazepines.

Different from this typical withdrawal SE is the entity known as subacute encephalopathy with seizures in chronic alcoholism (SESA) [161]. Affected patients are chronic abusers who present with progressive confusion, focal seizures, and focal neurologic deficits. There is no clear relationship between symptom onset and alcohol intoxication or withdrawal. The cause of the encephalopathy is not yet elucidated, but some authors have suggested that it might be due to frequent seizures or NCSE [162–164], which has been documented in at least 50% of cases. Focal neurologic signs include hemiparesis, neglect, and hemianopia. They are usually transient and might correspond to post-ictal phenomena. EEG findings include focal sporadic epileptiform discharges, focal slowing, lateralized periodic discharges (LPDs), and focal seizures and SE. Both temporal and extra-temporal seizures have been documented. Brain MR imaging often show transient T2/FLAIR/DWI cortical hyperintensities, likely of a peri-ictal nature, and chronic vascular changes [165]. CSF analysis is normal. Treatment is symptomatic, and response to anti-seizure medications is good.

Star Fruit (*Averrhoa carambola*) Intoxication

Star fruit contains several toxic substances, including caramboxin and oxalic acid [166]. Its ingestion may lead to delirium and SE, especially in patients with chronic renal failure [167, 168]. Brain MR imaging may show PRES or cortical T2/FLAIR/DWI hyperintensities, likely related to intense ictal activity. The mechanism is unclear and may include direct NMDA and AMPA receptor agonist activity or acute-on-chronic renal failure leading to PRES [169]. Treatment is supportive.

Posterior Reversible Encephalopathy Syndrome (PRES)

Posterior reversible encephalopathy syndrome (PRES) is a disorder of reversible subcortical vasogenic brain edema, currently believed to result from endothelial injury and blood–brain barrier dysfunction [170]. Common etiologies include acute renal failure, hypertensive crisis, shock, chemotherapy and immunosuppressive drugs, autoimmune disorders, sickle cell disease, and eclampsia. The typical manifestation is a syndrome of seizures, subacute encephalopathy, headache, and visual disturbances. Brain MR imaging with T2-weighted/FLAIR sequences is much more sensitive than non-contrast CT and shows bilateral vasogenic edema that typically predominates in the subcortical white matter of the parieto-occipital regions or along the superior frontal sulcus or in watershed areas. Involvement of the cortex, basal ganglia, thalamus, brainstem, and cerebellum is common. Small areas of restricted diffusion and intracranial hemorrhage can also occur in a minority of cases. Generalized tonic–clonic seizures occur in up to 75% of patients, but generalized convulsive SE is rare, complicating only 5–10% of cases. Complex partial and purely electrographic SE, often of posterior origin, also occurs, but its incidence has not been systematically studied [171–173]. EEG recordings often disclose bilateral independent occipital slowing, epileptiform or periodic discharges, and seizures [172, 174, 175].

Management of seizures and SE in PRES includes both anti-seizure medications and treatment of the underlying etiology, including the elimination of the causative agent and tight blood pressure control.

New-Onset Refractory Status Epilepticus of Unknown Etiology

In up to 15% of cases, the cause of SE remains unknown. Recent studies have drawn attention to de novo refractory status epilepticus syndromes of unclear origin in both children and adults, often preceded by a mild febrile illness [16, 17]. These syndromes have received various names, including new-onset refractory status epilepticus (NORSE) in adults [16]; febrile infection-related epilepsy syndrome (FIRES) [17], devastating epileptic encephalopathy in school-aged children (DESC) [176], and acute encephalitis with refractory repetitive partial seizures (AERRPS) [177] in school-aged children; and idiopathic hemiconvulsion-hemiplegia and epilepsy (IHHE) [178] syndrome in infants. Most authors believe that these syndromes belong to the same spectrum of acute encephalopathy with inflammation-mediated status epilepticus [179, 180]. They are characterized by the sudden onset in an otherwise healthy individual of frequent seizures and status epilepticus, often bilateral or multifocal. A nonspecific febrile illness with gastrointestinal, upper respiratory, or flu-like symptoms precedes the onset of seizures in most cases. CSF analysis and MRI often show changes suggestive of encephalitis (e.g., mild lymphocytosis, elevation of protein level, and T2/FLAIR hyperintensities in neocortical or mesial temporal structures), but no causative mutation, virus, or antibody is found despite extensive investigations. The etiology of these syndromes is unknown, but the presence of elevated levels of cytokines in the cerebrospinal fluid (CSF) [181] and inflammatory infiltrates in brain biopsy [182] of children with AERPPS suggests that it might be due to an intrathecal excess of inflammatory molecules, perhaps triggered by a

viral infection. This hypothesis is supported by experimental evidence that cytokines are powerful triggers of seizures in animals. Status epilepticus is usually highly refractory and can last for weeks. Mortality is high and most survivors develop pharmaco-resistant epilepsy. Long-term cognitive impairment is frequent, but some patients make a full recovery [5, 183]. Treatment with anti-seizure medications and anesthetics is often disappointing, but immune therapies and the ketogenic diet may be effective treatments.

A Practical Approach to Uncommon Causes of Status Epilepticus

Close to 200 different disorders have been reported to cause SE, and up to 50% might require specific therapy beyond anti-seizure medications. Knowledge of these conditions is of critical importance to ensure appropriate work-up and treatment.

Because of the diversity of possible causes, however, finding the underlying etiology can be a baffling process for a clinician unfamiliar with SE, especially in acute situations and outside of a tertiary care facility. A standardized systematic approach is thus necessary and has been shown to perform quite well in practice [4].

A careful history and a detailed physical and neurologic examination remain irreplaceable steps toward a correct diagnosis. They should focus on identifying specific risk factors, prodromal symptoms, and associated clinical signs suggestive of specific etiologies (see Table 8.4).

Brain imaging with MRI and CSF analysis should be performed in all patients without a clear etiology. Brain MRI improves diagnostic accuracy in a substantial number of cases, as PRES, small neoplasms, and brain abscess may be overlooked on CT images [4]. Frequent or prolonged seizures can cause nonspecific peri-ictal changes in the cerebral cortex, posterior thalamus, hippocampus, or corpus callosum on diffusion-weighted and T2/FLAIR images [184]. They should not be mistaken for evidence of encephalitis.

CSF analysis is essential for the diagnosis of inflammatory and infectious disorders. A mild to moderate pleocytosis or a mildly elevated protein level do not necessarily imply an infectious diagnosis, as this can be due to a neoplastic or autoimmune encephalitis, or even SE itself [185]. Several autoimmune encephalitides can only be diagnosed by the identification of a causative antibody in the CSF. The increasing recognition of an association between various autoimmune disorders and SE, especially refractory SE, as well as the beneficial response to various immunosuppressive treatments observed in some patients [186], should make the diagnosis of these autoimmune conditions a priority in patients with SE of unknown origin.

Conclusion

Unusual causes of SE are many and cover a broad range of inflammatory and autoimmune disorders, uncommon infections, rare genetic and congenital conditions, and several toxic and iatrogenic disorders. Autoimmune encephalitis in particular is increasingly recognized as an important cause of SE and benefits from immune therapies. Similarly, infections and inborn errors of metabolism require specific treatment beyond seizure control. A structured approach, relying on careful history and examination, CSF analysis, and brain MRI are fundamental to orient management and prioritize further work-up. Despite our increasing awareness and the availability of extensive testing, the cause of SE remains unknown in a substantial proportion of cases. These entities of cryptogenic SE, referred to as NORSE in adults and FIRES in children, often prove utterly difficult to control and remain a major clinical challenge. Further research is required to understand the cause of these conditions. An inflammatory mechanism is suspected, and some patients may benefit from immune therapies.

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Clinical Consequences of Generalized Convulsive Status Epilepticus

9

Vincent Alvarez and Andrea O. Rossetti

Introduction

Status epilepticus (SE) is the second most frequent potentially fatal neurologic emergency after stroke, with an incidence of 10–40 cases per 100,000 people per year [1, 2]; these figures are increasing over the past several years [3], probably due to better recognition and ascertainment. Rapid and effective treatment is essential [4], but SE is heterogeneous, and a refined knowledge of prognostic factors may not only orient caregivers and relatives, but also facilitate a tailored treatment strategy that maximizes efficacy and minimizes risks of side effects. This chapter focuses on the primary and secondary generalized convulsive forms of SE (GCSE), which imply generalized tonic–clonic movements of the limbs and mental status impairment (lethargy, confusion, and coma) [4], at least at initial presentation. GCSE represents about half of SE treated in acute facilities [1, 2, 5, 6]. In addition to seizure type, many other factors influence mortality and functional outcome, such as demographics, consciousness impairment, SE duration, underlying etiology and, last but not least, treatment. All these predictors will be addressed here after a brief overview of the consequences of SE. Finally, we discuss how these factors have been included in prognostic scores, and how they may be of help in daily practice.

Physiopathology of Neuronal Damage: A Micro- and Macroscopic Perspective

Status epilepticus is the clinical expression of self-sustaining seizure activity in neuronal networks. Initially, protein phosphorylation and modulation of ion channels and neurotransmitters are at play. Later, receptor trafficking and neuropeptide modulation may produce maladaptive changes [7]. An SE animal model with injection of bicuculline in baboons was developed more than 40 years ago [8], demonstrating that SE can induce ischemic changes in neurons, particularly in the cerebral cortex, hippocampus, cerebellum, and basal ganglia. The experiment was repeated on paralyzed and artificially ventilated animals to control for the role of systemic complications, showing the impact of the seizures themselves [9]. Neuronal damage was less severe in these control animals than in the unparalyzed baboons, but the pattern of involved brain regions was similar. A comprehensive review published more than 25 years ago proposed a schematic representation of neuronal injury [10]: glutamate induces a calcium influx into neurons, unleashing mitochondrial dysfunction, protease and lipase activation, and an increased activity of glutamate receptors, maintaining the cascade.

Recently, it has been demonstrated that programmed neuronal cell death is also induced by SE [11, 12]. Glia participation in neuronal damage has also been emphasized [13].

These animal models also highlight changes on a systemic level [14]. Body temperature and systolic blood pressure rise rapidly (within a range of 2–5 °C), along with an increase in cerebral and arterial PCO_2 and a fall in arterial and venous pH. While there is no experimental model of human SE, acidosis, hypoxemia, hyperglycemia, leukocytosis, and hyperpyrexia may all contribute to neuronal injury and an unfavorable outcome after SE [10, 15]. An increase in serum neuron-specific enolase (NSE) has been reported in a small cohort of SE patients [16], including with nonconvulsive forms [17], suggesting that seizures may by themselves induce neuronal death. Hippocampal abnormalities have been described in MRIs of 22 out of 199 children after febrile SE [18]. In adults with prolonged SE, diffusion-weighted MRI alterations have been described, sometimes leading to brain atrophy, laminar necrosis, or mesial temporal sclerosis [19]. Figure 9.1 provides an

V. Alvarez (✉) · A.O. Rossetti
Service de Neurologie, CHUV (Centre Hospitalier Universitaire Vaudois), Rue du Bugnon 46, 1011 Lausanne, Switzerland
e-mail: vincent.alvarez@hopitalvs.ch

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example of severe brain atrophy after prolonged SE due to a small traumatic brain contusion that one of the authors observed. Conversely, a study of 20 patients and 20 controls showed that after generalized convulsive SE (with a median duration of 1 h, 45 min), there was no change in MRI volumetry after 1-year follow-up [20]. This suggests that SE does not invariably lead to neuronal injury and cerebral atrophy—at least at the macroscopic level, and that other, yet unidentified modifying factors may be at play. (See also Chap. 10, "Neuropathology of Generalized Convulsive Status Epilepticus" and Chap. 25, "Consequences of Non-convulsive Status Epilepticus: Experimental and Clinical Evidence.")

Mortality After Generalized Convulsive Status Epilepticus

Mortality

The most frequently studied clinical outcome is mortality. Several different observational cohorts, population-based studies, or hospital discharge databases provide information about fatality rates following SE. Most focused on short-term mortality, e.g., at the time of hospital discharge, or at 1 month. Due to study design and inclusion criteria, however, the fatality rates are remarkably varied, ranging from 3–9% [21, 22] to 19–39% [23, 24]. The four studies cited were very different, the first two derived from nationwide hospital discharge databases, and the other two prospectively collected data from a single center and in a population-based assessment, respectively. Another very important factor is whether studies include children or not; mortality is usually lower in children than in adults, probably due to differences in etiologies and, to a lesser extent, comorbidities [25]. For example, a population-based assessment performed in French-speaking Switzerland that included children reported a mortality rate of 8% [1], while rates of 9–37% were found in two studies with similar design but including adults alone [24, 26]. It is also important to note that post-anoxic myoclonic SE has been included in some analyses—which may dramatically increase mortality rates, because most patients with this condition ultimately die [27]. As an example, the study by DeLorenzo et al. [2] which included patients with anoxic brain injury, reported a mortality rate of 22%, while a recent multicenter prospective cohort excluding post-anoxic cases reported a rate of 12% [28]. Table 9.1 provides information about mortality rates across different studies. An overall 10–15% short-term fatality rate appears reasonable to expect following GCSE in adults.

Few studies address the long-term effect of SE on mortality. A population-based survey in Rochester, Minnesota reported that more than 40% of patients who survived for the first 30 days after SE had died by the time of 10-year follow-up [29], representing a threefold increase in mortality

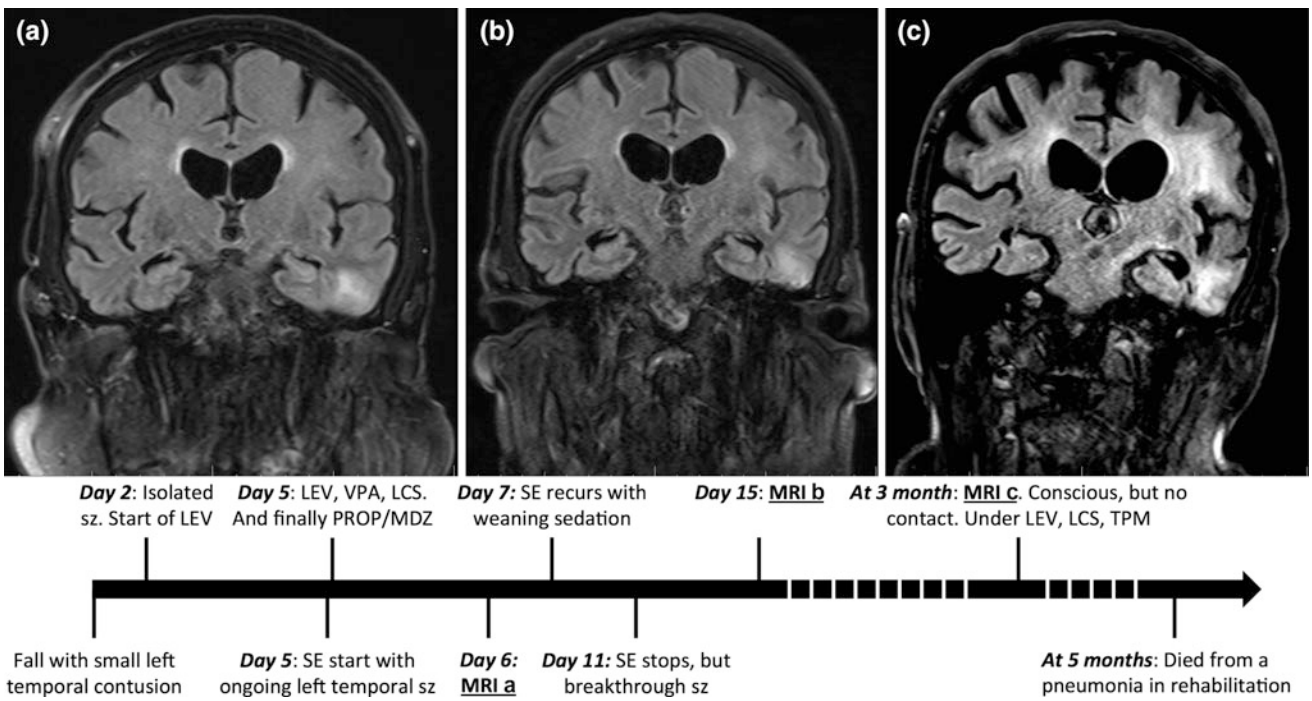

Fig. 9.1 Magnetic resonance imaging alterations (**a–c**) in brain atrophy after severe super-refractory status epilepticus. *LEV* levetiracetam; *VPA* valproic acid; *LCS* lacosamide; *PROP* propofol; *MDZ* midazolam; *TPM* topiramate; *MRI* magnetic resonance imagery; *sz* seizure

Table 9.1 Short-term mortality rate among different studies after status epilepticus

Author	Year	Design	Children	Anoxic	Mortality (%)
DeLorenzo et al. [2]	1996	Prospective population-based (VA, USA)	Yes	Yes	22
Logroscino et al. [23]	1997	Retrospective population-based (Rochester, MN, USA)	Yes	Yes	19
Coeytaux et al. [1]	2000	Prospective population-based (French-speaking Switzerland)	Yes	No	7.6
Knake et al. [26]	2001	Prospective population-based (Hessen, Germany)	No	Yes	9.3
Wu et al. [25]	2002	Statewide (CA, USA) hospital discharge database	Yes	Yes	10.7
Vignatelli et al. [24]	2003	Prospective population-based (Bologna, Italy)	No	Yes	37
Alvarez et al. [28]	2014	Prospective multicenter hospital cohort (MA, USA, and Lausanne, Switzerland)	No	No	12.8
Dham et al. [22]	2014	National-wide (USA) hospital discharge database	Yes	Yes	9.2

MA Massachusetts; *MN* Minnesota; *VA* Virginia; *USA* United States of America

as compared to that in a matched population without SE. All seizure types were included, 47% with GCSE. Another study including mostly GCSE (76.4%), reported a mortality rate of 20% at 12 years [30]; but follow-up data were available for only 32% of SE survivors, and the proportion of GCSE in follow up was not reported, suggesting that this might be a substantial underestimation of mortality.

Factors Associated with Mortality

Mortality rates after SE may depend significantly on demographic features, on the different types and causes of SE, and on different approaches to treatment.

The Patient: Some demographic factors such as gender appear to have no clear influence on mortality [31], but race may have a role: one study found an higher frequency of SE in non-whites as opposed to Caucasians (71 vs. 23 per 100,000 people, respectively) across all age categories, but especially in the very young and in the elderly. Mortality, however, was higher in Caucasians (31% vs. 17%) [2]. In several studies, increased age has been associated with mortality, with fatality rates increasing from 1% in the age group 1–19 years old, up to 47% in older groups (>65 years) [29]; being over 65 years old was associated with a 5.4 odds ratio (OR) for mortality after correction for most known confounding factors [32]. Of note, increased age is not only associated with higher mortality but also with a higher incidence of SE [2, 25], probably due to the increased burden of structural brain lesions (strokes, tumors, etc.).

Furthermore, medical comorbidities increase with age, but there are only a few studies addressing this topic. One US hospital discharge database indicated that patients with a greater number of comorbid conditions have a worse outcome [21], but this study had several limitations, including retrospective design and use of coded diagnoses. A prospective European study found that comorbidities, quantified using the Charlson Comorbidity Index [33], had only a marginal impact on SE mortality when others important factors were accounted for [34].

The Seizures. Seizure semiology is an important factor. While in absence SE the response to anti-seizure drugs is usually prompt and the outcome usually excellent [35], a mortality of up to 67% has been reported in nonconvulsive SE in coma [36]. GCSE lies somewhere in between. There was a mortality rate of 27% in a US population-based study of adult patients [2]; 21% in a retrospective hospital cohort from Turkey [37]; 10.1% in a subgroup analysis of a prospective hospital cohort of patients in Massachusetts and Switzerland [5]; 9% in a prospective cohort in western France [38]; and as low as 3.5% in the US hospital discharge database [21]. Even within a single seizure or SE type, mortality may vary remarkably. Based on these numbers, a reasonable estimate of mortality after GCSE is around 10–15%.

Analysis of the impact of SE duration has generated conflicting results. One study found a strong association between worsened outcome and a threshold of 1 h SE duration [39], while another study showed that while survival was better if SE lasted less than 10 h, SE duration lost its predictive value for poorer outcome once etiology, presentation in coma, and type of SE were accounted for [40]. This suggests that SE duration exerts probably a minor independent prognostic role.

Refractory SE (RSE), defined as ongoing clinical or electrical seizures despite two adequate lines of treatment (a benzodiazepine followed by a non-sedative anti-seizure drug) [4], confers a high rate of mortality; studies focusing on RSE report mortality rates ranging from 16.7 to 39% [41–43] (Table 9.2). Super-RSE (SRSE), corresponding to persistence of seizures even after 24 h of coma induction [44], seems to herald an even worse outcome. Unfortunately, and probably due to the relatively low incidence of SRSE, comprehensive data are sparse, relying mostly on case series and small cohorts not limited to GCSE [45–49]. As shown in Table 9.3, however, a relatively favorable outcome is

Table 9.2 Short-term mortality rate among different studies focusing on refractory status epilepticus

Author	Year	Design	Mortality (%)
Holtkamp et al. [41]	2005	Retrospective cohort (83 SE episodes) (Berlin, Germany)	16.7
Novy et al. [42]	2010	Prospective cohort (128 SE episodes) (Lausanne, Switzerland)	39
Sutter et al. [43]	2013	Retrospective cohort (111 SE episodes) (Basel, Switzerland)	38

Table 9.3 Outcome after super-refractory status epilepticus

Author	Year	Median SE duration with range	Mortality (%)	Comment
Holtkamp et al. [45]	2005	17 days	14	5/6 survivors were severely dependent
Cooper et al. [46]	2005	18 days (7–67)	57	2 survivors were functionally independent
Drislane et al. [47]	2011	5 days (4–59)	n/a (focused on survivors)	Older age, multiple medical illnesses, and coma (but not duration) associated with mortality
Kibride et al. [48]	2013	30.7 (8–169)	33	22% with good outcome (modified Rankin Scale 0–3)
Hocker et al. [49]	2013	4 (1–90)	37	8 of 34 survivors regained premorbid state

possible even after very prolonged SE durations, but mortality rates are still around 30%, with most survivors suffering from new morbidity.

The role of level of consciousness has been well established in several studies [32, 36, 40, 42]. For example, an increase of mortality with an OR of 3.03 has been reported for each decrease in the level of consciousness, from aroused, confused, to stuporous or comatose [32].

Electroencephalography (EEG). Some studies indicate that EEG background organization and sleep architecture correlate with preserved cognition and brain metabolism [50], suggesting that EEG might provide clues for outcome prediction. There are conflicting results in the literature. Ictal discharges occurring after SE, burst-suppression patterns and, to a lesser extent, lateralized periodic discharges, have been associated with higher mortality [51]; but in that study, 20% of patients had post-anoxic SE. Another retrospective analysis that did not control for confounding factors found an increased mortality in patients with lateralized periodic discharges [52]. More recently, a prospective assessment using validated EEG terminology found that EEG background (including posterior dominant rhythm and sleep architecture) were the only reliable outcome predictors after correction for SE severity and etiology [53]. Of note, lateralized periodic discharges were associated with an increased mortality in patients without brain injury in a case-control study of patients undergoing EEG monitoring [54].

The Etiology. Many demographic and clinical aspects are major determinants of mortality after GCSE, but the most important one is probably the underlying etiology itself [55]. In two epidemiologic studies, mortality related to SE due to low levels of anti-seizure drugs in patients with epilepsy was 4% [2] and 2% [25], as opposed to 33% with SE and central nervous system (CNS) infections, or 25% with stroke [25]. To address its independent role in SE outcome prediction, etiology has often been categorized as acute or not [2, 23, 32, 56], with some studies reporting an increased mortality for patients with an acute etiology, with ORs ranging from 0.4 [23] to 2.2 [56]. Of note, loss of predictive value after adjustment for other factors has also been reported [32]. This is probably due to the marked heterogeneity of "acute" etiologies, which include medication non-adherence and alcohol withdrawal, but also acute brain injuries such as stroke, hemorrhage, acute brain infections, and head trauma. To overcome this concern, categorization according to "potentially fatal" etiologies (including: acute large vessel ischemic stroke, acute cerebral hemorrhage, acute central nervous system infection, severe systemic infection, malignant brain tumor, AIDS with CNS complications, chronic renal insufficiency requiring dialysis, systemic vasculitis, metabolic disturbance or acute intoxication sufficient to cause coma in the absence of SE, eclampsia, and intracranial tumor surgery) has been proposed [32]. This approach produced a more robust predictor of mortality, with an OR of 11.7 [32], 6.9 [5], or 5 [57] in different studies.

Because etiology is such an important outcome predictor and because 42% of SE are related to an underlying etiology that requires tailored treatment (in addition to anti-seizure drugs) [28], identification of the etiology of SE should be one of the main objectives of SE management in the acute setting.

The Treatment. There is evidence that treatment guidelines are relatively poorly followed in daily clinical practice [5, 38, 58, 59]. While adequate first-line treatment is strongly associated with interruption of SE [38], its impact on mortality remains unclear. One study found that "insufficient treatment" was more frequent in the non-survivor group than in survivors (45% vs. 22% respectively) [60]. Better medical management was strongly and independently related to better clinical outcome (OR 21.09) in an Italian study comparing a peripheral and a university hospital [6]. Conversely, a Canadian cohort reported a comparable outcome between patients with or without "appropriate" treatment [61]. Finally, adherence to treatment guidelines, assessed by deviations from drug treatment sequence or dosages (±30% of the recommended doses) did not appear to have a significant impact on mortality [55]. While to our knowledge, this was the only study to include all known predictors in statistical models (demographics, etiology, SE severity, comorbidity, and treatment adequacy), it should be acknowledged that the definition of "treatment deviation" is critical and varies significantly from one study to the next.

Therapeutic coma using anesthetic drugs is recommended when second-line anti-seizure drugs fail to control seizures [4], but the evidence supporting this practice is sparse [62] and there are potentially serious side effects [63]. Some observational cohorts have questioned this practice. One was a retrospective assessment of 126 SE patients treated in ICUs in Baltimore [64]. The use of anesthetic drugs was associated with an increase in mortality (OR: 8.65), after adjustment for age, de novo SE, and etiology. Another study, of a prospective cohort of 171 patients with SE treated in the ICU in Basel, Switzerland, found a 2.9-fold relative risk of death when anesthetic drugs were used [65]. Of note, SE duration, severity of SE, use of further non-anesthetic antiseizure drugs, critical medical conditions, and etiology were considered in the analysis. Therapeutic coma was associated with poorer outcome (relative risk ratio for mortality, 9.10) in a prospective cohort of 467 patients in Lausanne, Switzerland [66]; the effect was greater in patients with focal as compared to GCSE, or nonconvulsive SE in coma. Demographics, etiology, impairment of consciousness, SE severity, treatment latency, and comorbidities were accounted for. Another study concentrating on de novo refractory SE, however, did not confirm these results [67], even after adjustment for SE severity, burden of complications, and SE duration. It remains difficult currently to distinguish between confounding by the treatment indication and the negative effects of intubation and coma induction. Nevertheless, a prospective controlled study would be very difficult to plan and carry out in this setting.

Why Do Patients Die After GCSE?

Unfortunately, while all studies report mortality rates after SE, information regarding reasons for death is missing. One study attempted to address these details [68], based on 920 SE patients managed in a single center over 10 years. The vast majority (78.8%) had GCSE. Of 120 deaths, 65.8% were attributed to underlying illnesses alone; the underlying etiology was *not* involved in the explanation of death in only 14 cases. In that subgroup, death was related to coma or treatment complications.

Functional Outcome in Survivors of Generalized Convulsive Status Epilepticus

Little attention has been directed to functional outcome after GCSE, as compared to mortality. Different functional outcomes have been investigated.

Studies with Cognitive Scales

To date, there are only two studies with well-documented cognitive measurements obtained both before and after SE. Both describe cohorts of patients living with epilepsy. In the first [69], only mild intellectual consequences were reported in nine adult patients with SE (four in GCSE) in comparison to nine control patients without SE. The second study [70] failed to demonstrate any changes in cognitive measurements from before to after SE in 15 patients, nor in 40 matched patients with epilepsy, but without SE, during the same period. Of note, most patients had secondarily generalized tonic–clonic seizures and a median duration of SE of 240 min.

Global Functional Scales

Some studies assess SE functional outcome using more rudimentary scales, such as the Glasgow Outcome Scale (GOS). A multicenter prospective cohort study from France with 177 GCSE patients, found that 18.8% were dead at

3 months follow-up; half of the survivors had severe functional impairment; 42.5% had a good outcome, with a GOS of 5 (i.e., the patient was able to return to work or to school). Longer seizure duration, cerebral injury, and RSE were strongly associated with poorer outcomes [71]. A single center retrospective study assessed 83 SE episodes and found that of 69 survivors, 16 (23%) had a deterioration of at least one point on the GOS at discharge compared to that on admission. Factors associated with functional deterioration after multiple logistic regression were acute symptomatic seizures and length of hospitalization [72]. Finally, one study used the modified Rankin Scale (mRS) to evaluate functional outcome after RSE: out of 63 SE episodes, poor functional outcome (mRS 4–6) occurred in 76.2%, and only 8 (12%) regained their premorbid status [49]. Of note, a few patients improved several months after the acute facility discharge. Duration of drug-induced coma, cardiac arrhythmia requiring intervention, and lung infection were associated with poor functional outcome.

Risk of Developing Epilepsy After a De Novo SE

Another outcome of interest after de novo SE is the risk of developing epilepsy: SE appears to increase the odds for subsequent unprovoked seizures 3.3-fold as compared with initial brief acute symptomatic seizures, after controlling for age, gender, and cause [73], but a specific role for the generalized convulsive form of SE remained uncertain because the majority (41%) had a SE with focal seizures and only 23% of patients had GCSE. More recently, in a prospective cohort of 89 patients with de novo SE, 58.7% had recurrent seizures after a median follow-up of 10 months [74]. After multivariable analysis, development of subsequent epilepsy was associated with SE lasting more than 24 h only, with an OR of 3.8. This is in line with a previous finding that secondary epilepsy was more frequent after RSE than non-refractory SE [41].

Return to Premorbid Baseline

Finally, a functional outcome assessed in some studies is the "return to premorbid baseline", meaning that the patient's functional status at hospital discharge is the same as before the SE episode. This outcome measurement, however, is somewhat subjective and maybe imprecise, because complete recovery is often difficult to prove. Nevertheless, among 27 patients with SE due to alcohol abuse, most patients (81.5%) returned to their clinical baselines at discharge [75]. It was also pointed out that a potentially fatal etiology (see above) was less common in patients returning to their premorbid conditions (34.3%) than in patients who did not return to baseline (72.1%) [32]. These two studies emphasize, once again, the cardinal role of etiology in the likelihood of returning to the patent's premorbid baseline. Our group also showed that increased age, more severe SE, and an increased load of comorbidities, decreased the probability of regaining a patient's clinical baseline, and conversely, that neither the choice of second-line anti-seizure therapy nor adherence to treatment guidelines influenced this outcome [55, 76]. The EEG may also provide some information: the finding of normal stage 2 non-REM sleep patterns (such as K complexes and spindles) is associated with an odds ratio of 2.6 favoring a complete recovery [53].

Perspective

It is important to note that as opposed to mortality, functional outcome has received much less attention. Mortality appears to be influenced mainly by "non-modifiable" factors such as etiology, demographics, and seizure type, and there is a lively debate about the pros and cons of aggressive treatment using general anesthetics [77]. As such, detailed neuropsychological assessment, clinical scores as the modified Rankin scale, or even outcomes as simple as "return to previous work status" and "previous driving ability," should be considered in future SE studies.

Table 9.4 Status Epilepticus Severity Score (STESS), a favorable score is 0–2

	Features	STESS
Consciousness	Alert or somnolent/confused	0
	Stuporous or comatose	1
Worst seizure type	Simple-partial, complex-partial, absence, myoclonic[a]	0
	Generalized convulsive	1
	Nonconvulsive status epilepticus in coma	2
Age	<65 years	0
	≥ 65 years	2
History of previous seizures	Yes	0
	No or unknown	1
Total		0–6

From Rossetti et al. [79] with permission, adapted from data in Rossetti et al. [32]
[a]Complicating genetic (idiopathic) generalized epilepsy

Outcome Prediction Models

Based on the known predictors and prediction models discussed above, some authors have provided scoring systems to be used in helping clinicians guide their decisions in daily practice.

The STESS

The first published such score is the STESS, *STatus Epilepticus Severity Score* [78, 79]. It includes 4 variables (Table 9.4): age (<65 years = 0 points; ≥ 65 years = 2 points); seizure type (simple-partial, complex-partial, absence, and myoclonic in the context of idiopathic/genetic epilepsy = 0; generalized convulsive SE = 1; nonconvulsive SE in coma = 2); level of consciousness before treatment (alert, somnolent or confused = 0; stuporous or comatose = 1); and history of previous seizures (yes = 0; no = 1), with a total score between 0 and 6 points. Of note, "history of previous seizure" is a rough but easy-to-use surrogate for etiology. Most survivors (97%) and only 3% of patients who died had a favorable STESS score (between 0 and 2); a score of 3–6 was found in 61% of survivors and in 39% of non-survivors. Thus, the STESS score has excellent negative predictive value (0.97) for mortality, and two independent studies have validated its prognostic precision [36, 80]. STESS is an easy-to-use, validated score, based on clinical variables immediately available at the bedside at the time of presentation, and can be used in clinical research to stratify patients according to SE severity.

The EMSE

More recently, the EMSE (Epidemiology-based Mortality Score in Status Epilepticus) was published [81]. Based on epidemiologic data available in the literature, the authors developed a score that included etiology, age, comorbidity, EEG, SE duration, and level of consciousness (Table 9.5). Each variable was given a different weight (0–60), reflecting that factor's likely correlation with the mortality rate. Based on one evaluation of 92 patients, EMSE seemed to perform better than the STESS score to predict mortality or favorable outcome. Still, the EMSE requires some information not readily available in early management, such as the precise etiology (which may be hard to determine, at least initially) and EEG data. Also, it appears less convenient to use at the bedside, but it might provide interesting data in clinical research to stratify patients.

Table 9.5 Epidemiology-based mortality score in status epilepticus (EMSE)

			Points :
Etiology	CNS - Anomalies	2	
	Drug reduction / withdrawal, poor compliance	2	
	Multiple sclerosis	5	
	Remote cerebrovascular disease, brain injury	7	
	Hydrocephalus	8	
	Alcohol abuse	10	
	Drug overdose	11	
	Head trauma	12	
	Cryptogenic	12	
	Brain tumor	16	
	Metabolic: sodium imbalance	17	
	Metabolic disorder	22	
	Acute cerebrovascular disease	26	
	CNS-infection, acute	33	
	Anoxia	65	
	Choose one etiology	→	=
Age	21-30	1	
	31-40	2	
	41-50	3	
	51-60	4	+
	61-70	5	
	71-80	6	
	>80	7	
	Choose one age category	→	=
Comorbidity	Myocardial infarction, congestive heart failure, peripheral vascular disease, cerebrovascular disease, dementia, chronic pulmonary disease, connective tissue disease, ulcers, mild liver disease, diabetes	10	
	Hemiplegia, moderate to severe renal disease, diabetes with end organ damage, any tumor including leukemia/lymphoma	20	+
	Moderate to severe liver disease	30	
	Metastatic solid tumor, AIDS	60	
	Add different comorbidities	→	=
EEG:	Burst-suppression (spontaneous)	60	
	After status ictal discharges	60	
	Lateralized periodic discharges	40	+
	Generalized periodic discharges	40	
	None of above	0	
	Choose one EEG feature	→	=
			↓
TOTAL	*Total when adding the 4 categories score*		=

CNS central nervous system; *EEG* electroencephalogram (adapted from Leitinger et al. [81] with permission)

Conclusions

Status epilepticus is a heterogeneous condition, even when focusing on GCSE alone. Overall, a mortality of 10–15% may be expected after GCSE, and even higher in cases of refractory GCSE. Etiology is by far the most robust predictor of outcome, so finding the cause of the seizures should be considered a priority almost as urgent as inducing its cessation. Other factors such as increasing age, impairment of consciousness, EEG findings and, to a lesser extent, SE duration, can be considered in making decisions regarding treatment aggressiveness in cases of refractory or super-refractory GCSE.

The optimal way of implementing prognostic scores (STESS and EMSE) in clinical practice has not yet been determined, but it appears reasonable to include an early prognostic orientation in decisions regarding treatment strategies. For example, a patient with a catastrophic etiology such as neoplastic meningitis will probably not benefit from aggressive treatment but has relatively little to lose in terms of side effects. One attempt at balancing the risks and benefits of aggressive treatment of SE has been published recently [82] and takes these outcome predictors into account. Ultimately, the target for clinical management is to tailor each therapeutic intervention to the individual patient, taking into account not only the immediate clinical presentation, but also the comorbidity background, the underlying etiology if known, and the patient's advanced directives and the family's wishes. Treatment of generalized convulsive status epilepticus remains a sort of art, and the role of clinical researchers is to provide a valid rationale on which to base the treatment and management.

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Neuropathology of Generalized Convulsive Status Epilepticus

10

Nathan B. Fountain and Suchitra Joshi

Introduction

The neuropathology of status epilepticus is well established. This chapter will review the histopathology and pathophysiology of cellular damage associated with generalized convulsive status epilepticus (GCSE) based on observations from human cases and experimentally induced status epilepticus (SE). The mechanisms currently thought to cause cell death will be discussed. This chapter concentrates on human 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, 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 (see Chap. 9, "Clinical Consequences of Generalized Convulsive Status Epilepticus").

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.

N.B. Fountain (✉) · S. Joshi
Department of Neurology, University of Virginia,
Box 800394, Charlottesville, VA 22908, USA
e-mail: nbf2p@virginia.edu

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Neurologic Deficits as Evidence of Neuronal Injury

The incidence of specific neurologic findings after GCSE is surprisingly sparse. Dodrill and Wilensky reported a prospective study of nine epilepsy patients with SE and matched epilepsy patient controls and found a trend toward decline in three of four tests of mental ability administered [1]. 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 9–11% 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].

Epileptogenicity of Status Epilepticus

Generalized convulsive SE may cause epilepsy or be the presenting seizure in patients with epilepsy of another cause. The epileptogenic potential of GCSE has long been known [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 SE, 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 status rather than from the underlying etiology is more problematic. In a separate study, Hesdorffer and colleagues found a 3.3-fold increased risk for epilepsy after SE compared to the occurrence following a single acute symptomatic seizure [8]. At 10 years of follow-up, 41% of those with SE due to an acute symptomatic cause had epilepsy, compared to 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.

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 SE [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-month-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 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 weeks, 6 months, and 1 year after SE [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 status for longer than 2 h. Therefore, it is possible that the duration or severity of status 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 weeks later, and the other had an astrocytoma.

Biochemical Evidence of Neuronal Injury

There is biochemical evidence of neuronal injury during SE. Neuron-specific enolase is an intracellular enzyme 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 seizure, 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.

Characteristics and Distribution of Neuropathology

Hippocampal Histopathology

There is clear region-specific cell loss resulting from GCSE. Historically, the neuropathology of SE 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 eleven 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 SE, taken from a total of 290 brains of epilepsy patients [22]. The sample included eight children (six 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 in the dentate gyrus. Cerebellar Purkinje cell loss and acute reactive gliosis is 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 SE in two of the infants and eight of the adults. One could infer that adult neurons are less susceptible to status-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 of the adults. A more parsimonious explanation, however, is that the epilepsy patients died of systemic effects of status 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 status in the hospital without other significant contributing factors [27]. They found neuronal loss and gliosis in the hippocampus, amygdala, dorsomedial thalamus, Purkinje cells of cerebellum, and piriform and entorhinal cortices. Since these patients had only focal motor status, 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.

Extra-hippocampal Injury

There have been a few reports of more widespread cortical damage after SE, 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 she also had multiple medical problems including 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 not primarily due to SE.

Nonconvulsive Status Epilepticus

Nonconvulsive status epilepticus (NCSE) is considered in detail elsewhere in this volume. NCSE has received much attention as a clinical entity, but its pathophysiology has been neglected. This is not surprising because its very definition is controversial [31]. It may be reasonable to generalize the pathophysiology from GCSE to NCSE, but there is 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 of 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 23–46% 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, there are older reports of 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 found 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 SE or EEG findings. Thus, it remains unclear whether, or under what circumstances, NCSE leads to neuronal injury.

Animal Models of Status Epilepticus

The clinical relevance of human findings is indisputable, but insights into specific aspects of the neuropathology are provided by the added degrees of control in experimental animal models of GCSE. The most commonly used animal models include systemic administration of chemoconvulsants such as pilocarpine with or without lithium pretreatment [36, 37], kainic acid [38, 39], homocysteine after a focal cobalt lesion [40], and organophosphates [41–43],

though other agents such as bicuculline, pentylenetetrazol (PTZ), *N*-methyl-D-aspartate (NMDA), flurothyl, and allylglycine can also be used to induce SE [32] (Table 10.1). In addition to systemic administration, infusion of chemoconvulsants into hippocampus or amygdala also produces GCSE [44–46]. The pilocarpine and kainate models of GCSE not only replicate the clinical and electrographic features of human GCSE, but a majority of animals also develop recurrent spontaneous seizures following SE. Therefore, these models offer an opportunity to study mechanisms of epileptogenesis.

A disadvantage of chemoconvulsant models is that these agents themselves are toxic, and thus it is difficult to distinguish between their effects and those of the seizures. Furthermore, some of the agents such as bicuculline, picrotoxin, penicillin, kainic acid, and NMDA act on neurotransmitter receptors, which makes them unsuitable for studies aimed at understanding the alterations in the plasticity of neurotransmitter receptors during SE and for testing the novel therapeutic strategies which modulate inhibitory or excitatory neurotransmission or both.

Electrogenic models of SE were established to overcome the limitations associated with chemoconvulsants. Lothman and colleagues developed an electrical stimulation model of status epilepticus in which continuous electrical stimulation of the hippocampus triggers self-sustaining seizures that are restricted to the limbic system [47]. Electrical kindling of the amygdala or the stimulation of perforant path also produces SE [48, 49]. This stimulation model triggers neurodegeneration and the development of epilepsy, similar to that observed in pilocarpine or kainate models of SE.

Table 10.1 Chemoconvulsant models of status epilepticus

Systemic or intracerebroventricular
NMDA
Quisqualate
Kainic acid
Domoic acid
Pentylenetetrazol
Bicuculline
Allylglycine
Pilocarpine ± lithium
Soman
Flurothyl
Intracerebral
Kainic acid in amygdala
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

Altered Neurotransmission in Status Epilepticus

A balance between excitatory and inhibitory neurotransmission maintains the neuronal firing rate, and a disruption of this homeostasis is associated with seizures. The γ-aminobutyric acid type A (GABA-A) receptor mediates the majority of inhibitory neurotransmission in the brain whereas ionotropic glutamate receptor subtypes, including NMDA, α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA), and kainate, contribute the majority of excitatory neurotransmission. The hippocampus plays an important role in the generation and sustaining of seizures, and it is a main structure affected by SE. Therefore, studies in animal models of GCSE have focused on understanding alterations in the neurotransmission of hippocampal dentate granule cells (DGCs) and CA1 pyramidal neurons during SE.

Impaired Inhibitory Neurotransmission

DGCs are highly inhibited, and their intrinsic excitability is much lower than that of hippocampal CA1 pyramidal neurons. DGCs are proposed to restrict spread of excitatory activity to neurons of the hippocampus proper, but impaired inhibition of DGCs could allow seizure spread into the hippocampus. The GABAergic inhibition of DGCs is compromised in animals in SE [50–52]; the frequency of synaptic currents is reduced, and their amplitude is also smaller. In addition, GABAergic inhibition of CA1 pyramidal neurons of animals in SE is also attenuated [53–55]. The entorhinal cortex provides substantial input into the hippocampus. Thus, these alterations likely allow activity from the entorhinal cortex to spread into the hippocampus and follow a reentrant loop that sustains seizure activity.

Biochemical studies have found reduced surface expression of γ2 subunit-containing GABA receptors, which are clustered at the synapses in the hippocampi of animals in SE [51, 55]. Development of resistance to benzodiazepines, which are the commonly used first-line therapy for SE, is a significant clinical problem that is also replicated in animal models of SE [41, 51, 56, 57]. Benzodiazepines exert their action via γ2 subunit-containing GABA receptors. The reduced expression of functional γ2 subunit-containing

GABA receptors thus helps to explain a rapid reduction in the efficacy of diazepam to terminate SE [50, 53, 54, 58].

GABA receptors are constantly trafficked between the surface membrane and the intracellular pool. In a cell culture model of SE, repetitive action potential firing can be induced by incubation of cultures in a medium lacking Mg^{2+} ions or containing high extracellular potassium and NMDA. In these systems, the reduced surface expression of γ2 subunit-containing GABA receptors is associated with accelerated internalization of these receptors [51, 56, 59]. Similar to whole animal experiments, blocking the activity of protein phosphatases is sufficient to prevent the functional down-regulation of synaptic GABA receptors in cell culture models of SE [56]. Thus, preventing mechanisms that destabilize receptors at the surface membrane may provide targets to restore GABAergic inhibition.

Augmented Excitatory Glutamatergic Neurotransmission

Concomitant with reduced inhibitory neurotransmission, excitatory neurotransmission of hippocampal principal neurons mediated by NMDA and AMPA receptors is strengthened during GCSE [60]. There is internalization of GluA2 subunit-containing AMPA receptors during SE, which likely contributes to the calcium influx and activation of cellular signaling associated with cell death and epileptogenesis. The excitatory neurotransmission mediated by NMDA receptors is also augmented during GCSE [60]. Synaptic NMDA receptor-mediated currents recorded from DGCs of animals in GCSE were larger and had altered kinetics of decay. The cell surface expression of NR1 and NR2B subunits of NMDA receptors is also increased in the hippocampi of animals in GCSE.

Taken together, the dynamic movement of GABA receptors from the surface membrane toward intracellular compartments coincides with the insertion of NMDA and AMPA receptors into the surface membrane. Under normal conditions, mechanisms that maintain homeostatic synaptic plasticity ensure that when the network activity is enhanced, excitatory neurotransmission is downscaled and inhibitory neurotransmission is increased, such that the target firing rate is restored. Studies in animal models of SE, however, indicate that a failure in maintaining homeostatic synaptic plasticity contributes to prolonged seizures. If excitatory neurotransmission through AMPA or NMDA receptors is blocked, the seizures terminate [60–62]. NMDA antagonists also enhance the efficacy of diazepam, and a combination of NMDA antagonists and diazepam can be effective in terminating even prolonged SE [63, 64].

Histopathology of Experimental Status Epilepticus

Histopathologic investigations from electrogenic and chemoconvulsant models demonstrate patterns of cell loss identical to those in human GCSE. SE lasting for 30–60 min is sufficient to induce neuronal damage, and the severity of damage correlates with the duration of seizures [65]. Early immunohistochemical techniques, including Nissl and silver staining, have helped identification of gross morphologic changes and patterns of cell loss that occur following SE [37, 66, 67]. Subsequent studies that used fluoro-jade and TUNEL staining as well as expression of apoptosis marker proteins have provided additional insights into aspects of cell death triggered by SE [68].

Pattern and Evolution of Cell Death Following Status Epilepticus

The hippocampus is the region most susceptible to cell death following SE [41, 69, 70]. Extensive degeneration of CA3 and CA1 pyramidal neurons has been observed in different animal models of GCSE, whereas CA2 pyramidal neurons and DGCs are mostly preserved [65, 71–73]. In addition, middle layers of entorhinal cortex also suffer cell loss [74]. In these animal models, fluoro-jade, a marker of cell death, could be detected in hippocampal principal neurons as early as 3–4 days following SE. Additional cell loss may occur due to recurrent spontaneous seizures which appear following a seizure-free latent period of variable duration after SE.

GABAergic interneurons are also susceptible to neurodegeneration. Loss of inhibitory interneurons present in the hilus, particularly those expressing somatostatin, is observed in animal models of SE [75–78]. In contrast, parvalbumin- or cholecystokinin-positive interneurons are spared. This yields a complex modulation of inhibition, resulting in the net loss of the inhibitory inputs to the DGCs.

It is noteworthy that young animals are resistant to neurodegeneration following SE [79–81]. There is also a strong correlation between neurodegeneration following SE and the development of epilepsy, and young animals incurring minimal cell death following SE do not develop epilepsy [82].

Mechanisms Underlying Neurodegeneration

It is reasonable to consider that systemic factors, such as elevated body temperature, and oxygen and glucose supply to the brain that are insufficient to cope with the increased

demand of SE, may contribute to neurodegeneration. Cell death was still observed, however, in animals in which these parameters were maintained in the normal range during SE [83]. Instead, there is compelling evidence that glutamate-induced excitotoxicity plays a central role in cell death [84]. Canadian researchers reported that an acute neurologic syndrome, including seizures and SE, was due to ingestion of mussels from Prince Edward Island contaminated by domoic acid [85, 86]. Domoic acid is structurally similar to glutamate and probably activates glutamate-mediated excitation. Furthermore, blockade of NMDA receptors during experimental SE prevents cell death [87, 88]. Glutamate receptor-mediated calcium overload is likely to cause stress to mitochondria and endoplasmic reticulum, which also causes cell death [89, 90]. The breakdown of the blood–brain barrier during SE causes activation of glia and inflammation [91], which also appears to contribute to cell death.

Summary

The histopathologic damage induced by GCSE is straightforward based on human clinical, radiologic, and histologic studies 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. Because neuronal injury is ongoing as long as seizure activity continues, patients who do not awaken immediately after treatment of SE must undergo EEG to exclude NCSE or they risk potential neuronal injury.

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Focal Status Epilepticus

11

Lisa Knopf and Bernard S. Chang

Introduction

Focal status epilepticus (FSE) is a condition in which there is an electrically discrete, continuously discharging epileptic disturbance associated with a definable neurologic deficit or abnormal behavior. In contrast to generalized status epilepticus, where the epileptic discharges occur in a widespread synchronous fashion across the entire cortex, the discharges in FSE are limited to a single region and do not spread. Compared to the literature on generalized convulsive status epilepticus (GCSE), that on FSE is less extensive and is generally restricted to case reports and case series.

Electrographic FSE can arise from any discrete region of cortex. If FSE occurs in the temporal or limbic regions, it affects consciousness and is referred to as FSE with dyscognitive features (see Chap. 20, "Clinical Presentations of Nonconvulsive Status Epilepticus"). If it occurs in systems that subserve language function, an epileptic aphasia may result (see Chap. 21, "Cognitive Manifestations of FSE"). If it occurs in the occipital lobe, it can cause symptoms mimicking other conditions causing visual loss [1, 2]. If it occurs in an area of the brain involved in motor activity, focal motor status epilepticus occurs—often referred to as *epilepsia partialis continua* (EPC).

Motor signs are more easily seen and recognized than more subtle changes in cognition and perception, thus likely accounting for the observation that reported FSE is almost always focal motor in nature—and FSE has become almost synonymous with EPC.

This chapter deals primarily with EPC and its epidemiology, etiology, pathogenesis, differential diagnoses, clinical presentations, electroencephalogram (EEG) and imaging findings, and specific treatments. The chapter addresses other types of FSE briefly, but they are covered primarily in other chapters.

Definitions

EPC is defined as "spontaneous regular or irregular clonic muscular twitching affecting a limited part of the body, sometimes aggravated by action or sensory stimuli, occurring for a minimum of one hour and recurring at intervals of no more than ten seconds" [3, 4]. It has been studied from both an epilepsy and a movement disorder perspective. Thus, authors may also require demonstration of epileptiform EEG abnormalities (ideally in fixed temporal coupling to the muscle jerks) or abnormalities in other studies such as giant somatosensory evoked potentials (SSEPs) to demonstrate the cortical origin of the muscle jerks [5, 6].

Although not often used in clinical practice, the Bancaud classification system divided EPC into two groups based on underlying etiology: non-progressive (Type I), and progressive (Type II) [7], the latter associated eventually with worsening neurologic function and intractable seizures. The most common cause of Type II EPC is Rasmussen encephalitis, a pediatric neurologic disorder characterized by unilateral inflammation of the cerebral cortex [8–10].

Epidemiology

EPC is a relatively rare disorder. Cockerell and colleagues estimated its prevalence as less than 1 per million, based on 36 cases reported in the United Kingdom over a 1 year period, 10 of the cases being new [5]. A 14-year retrospective analysis of 76 cases of EPC in a tertiary care center in India found that about 5–6 cases of EPC were admitted each year in their hospital, a referral center admitting approximately 3000–4000 inpatients per year [11]. According to the same study, the male: female ratio was

L. Knopf · B.S. Chang (✉)
Comprehensive Epilepsy Center, Harvard Medical School, Beth Israel Deaconess Medical Center, 330 Brookline Ave, Kirstein 457, Boston, MA 02215, USA
e-mail: bchang@bidmc.harvard.edu

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46:30, the mean age of patients 30.2 ± 23.4 years, and the median age 26 years.

The epidemiology of frontal and temporolimbic status epilepticus is covered elsewhere (see Chap. 3, "The Epidemiology of Status Epilepticus"). There are far fewer reports of FSE occurring in nontemporolimbic and nonmotor systems, likely because other types of FSE (e.g., sensory or autonomic) are less easily recognized and often misdiagnosed.

Etiologies

The usual etiology of EPC is a focal lesion involving the cortex (usually sensorimotor cortex) that results from stroke, trauma, infection, metastasis, or a primary tumor. Hypoxic, metabolic, or infectious encephalopathies may provoke EPC in patients with prior focal lesions.

The three largest EPC case series available are still fairly small: with 32 [3], 40 [5], and 76 [11] patients. Nevertheless, their findings regarding the etiology of EPC are similar. A compilation of the results of these three series indicated the following etiologies: vascular disorders (24–28%), encephalitides (15–19%), neoplasms (5–16%), metabolic disorders (6–14%), and unknown (19–28%). A compilation of multiple case reports in the 1970s (with a total of 162 patients) yielded the following distribution: inflammatory disorders (32%), neoplastic disorders (19%), head trauma (16%), vascular disorders (14%), others (3%), and unknown (16%) [10]. Of note, this compendium of case reports may have a significant ascertainment bias, as EPC from a common etiology (e.g., stroke) is likely considered less noteworthy (and reportable) than that due to uncommon etiologies (e.g., neurocysticercosis).

From the three largest case series, then, the most common cause of EPC is vascular disorders, including stroke, intracranial hemorrhage, cerebral venous sinus thrombosis, and vasculitis [3, 5, 11]. The authors have seen cases in which EPC occurred in the setting of a remote vascular lesion along with an acute metabolic disturbance, such as hyponatremia; this suggests that adults, particularly elderly individuals, in whom no obvious vascular lesion is seen but a metabolic disturbance is identified as the cause of EPC [3], may actually have small occult ischemic lesions as a structural focus.

Infectious or inflammatory encephalitides comprise between 15 and 19% of cases [3, 5, 11]. In children, Rasmussen encephalitis is the most common cause of EPC [12, 13]. Infectious encephalitides associated with EPC include herpes simplex virus, tuberculosis, syphilis, toxoplasmosis, neurocysticercosis and progressive multifocal leukoencephalopathy in HIV. Multiple sclerosis, with inflammatory demyelinating brain white matter lesions, is also a reported etiology of EPC [14].

Neoplasms account for 5–16% of cases of EPC [3, 5, 11]. They are most often progressive glial tumors but also include hemangioblastoma, meningioma, lymphoma, metastatic lesions, or gliomatosis cerebri.

Metabolic disorders comprise another 6–14% of cases [3, 5, 11]. The most common of these is diabetic nonketotic hyperglycemia. In patients with prior focal cerebral damage, EPC may be the presenting feature or a later complication of nonketotic hyperglycemia [13, 15]. Occasionally, it is the presenting feature of diabetes [15] but more often occurs as the consequence of chronic diabetes coexisting with a central nervous system (CNS) structural lesion. Hyponatremia associated with nonketotic hyperglycemia appears to be the key metabolic derangement that predisposes to EPC: the presence of EPC is related to the severity of hyponatremia in an almost linear fashion [13]. Hepatic encephalopathy is another reported metabolic etiology [3].

In case reports, some medications, including antibiotics, have been associated with EPC [16], although as always it is hard to be sure about the causal relationship in these cases. Finally, mitochondrial disorders (such as myoclonic epilepsy with ragged red fibers [MERRF]) can present with EPC along with a spectrum of other symptoms [5, 11].

In children, the etiology of EPC is different. In a recent case series of 51 children, 52% of cases were caused by inflammatory and immune-mediated disease, most often Rasmussen encephalitis but also subacute sclerosing panencephalitis, CNS tuberculosis, limbic encephalitis, and multiple sclerosis [12]. Another 13.8% were due to metabolic disorders, including mitochondrial disorders, neuronal ceroid lipofuscinosis, and Menkes disease; 11.8% were due to structural brain abnormalities such as malformations of cortical development (e.g., focal cortical dysplasia, heterotopia, hemimegalencephaly, and lobar holoprosencephaly); 7.8% were labeled cryptogenic; 5.9% were attributed to dual pathologies; and finally, 2.8% were deemed postoperative EPC.

Pathophysiology

The pathophysiology of EPC is only partially understood, and multiple mechanisms have been proposed. In most cases, the origin is clearly cortical and localized to the motor strip, but corticothalamic loops have been proposed to be involved in the perpetuation of seizures, and subcortical seizure generators have also been postulated. In addition, there is research that attempts to explain why EPC can be so prolonged and refractory to anti-seizure medications, compared to other types of status epilepticus.

Initiation of EPC

The most widely supported (and most intuitively logical) hypothesis is that EPC is generated in the pyramidal cells of the motor cortex. This is supported by clinical and electrophysiologic evidence in human studies, and in animal research, where lesioning the central neocortex has been shown to produce EPC [17]. Back-averaging, which averages EEG events preceding the muscle jerks of EPC, has shown that a cortical epileptic discharge occurs consistently before the clinical appearance of the myoclonic jerk, with a latency suggesting that the cortically generated potential propagates down the corticospinal tract [5].

Nevertheless, cases of EPC occurring with subcortical lesions and seemingly preserved cortex suggest that subcortically generated EPC also occurs [18]. In these cases, the seizure generator is typically suspected to be in the thalamus, but this has not been shown conclusively to date.

Modulation and Propagation of EPC

Research also suggests an important role of the thalamus, and specifically thalamocortical circuits, in contributing to the long duration of some cases of EPC. For example, in a study of monkeys with EPC induced by aluminum hydroxide injection into the motor cortex, EPC terminated after the ventral posterolateral nucleus of the thalamus was lesioned [17]. In a patient with EPC, a fluorodeoxyglucose (FDG)-positron emission tomography PET scan demonstrated increased metabolic activity in both the motor cortex and the ipsilateral thalamus [18, 19]. Ipsilateral thalamic hyperintense diffusion-weighted imaging (DWI) lesions on magnetic resonance imaging (MRI) may be seen after prolonged FSE [20]. This is thought to result from excessive activity in thalamic nuclei that have reciprocal connections with the involved cortex, and as possible evidence of the role of the thalamus in the evolution of focal seizures into FSE.

There are also data to suggest that some basal ganglia circuits could be involved in modulation and interruption of EPC (and other forms of FSE). In a study of ring chromosome 20, a syndrome characterized by drug-resistant complex partial status epilepticus, patients were found to have decreased (18F) fluoro-L-Dopa uptake in the striatum during seizures, suggesting that a deficit in dopaminergic activity might keep the basal ganglia from being able to interrupt seizures in this specific patient population [21].

How EPC Remains Localized

Unlike other types of seizures, EPC can persist for long periods (sometimes up to years) while remaining well localized to a small group of muscles and a small region of the cortex. This may be due to the intrinsic properties of the neocortex, which possesses powerful lateral inhibition that is probably designed to keep motor responses precisely localized [22]. Therefore, EPC may be a unique expression of cortical organization [22–24].

By contrast, the temporolimbic system maintains connections to several associative areas of neocortex (as part of its role in memory encoding) and appears designed to spread excitability in a widespread fashion. This may explain why seizures of limbic origin seem less likely to remain finely localized [22].

Semiology

EPC is defined as the occurrence of almost continuous and rhythmic or semi-rhythmic muscle contractions (myoclonic jerks) that remain localized to a limited area on one side of the body. Compared to other forms of status epilepticus, EPC can be significantly more prolonged and can persist for hours, days, or even years [22, 23]. Consciousness is usually preserved in EPC, but post-ictal weakness is often present. Any muscle group may be involved, but distal musculature is more frequently affected. The myoclonic jerks may appear isolated or occur in clusters, with a regular or irregular appearance, at a frequency of 1–2 jerks per second. During each jerk, there is typically synchronous activation of both agonist and antagonist muscles on the affected side [23].

EPC most often involves the muscles of the upper half of the body. In a study of 151 patients presenting with EPC, the authors found that the seizures involved the head in 16% of patients, the head and upper limb in 14%, the upper limb alone in 40%, the trunk in 5%, the lower extremity in 14%, and the entire hemibody in 11% [11]. This may reflect the somatotopic organization of the motor cortex, where more space is devoted to the face and arm compared to the leg and trunk.

The myoclonic jerks in EPC occur spontaneously, but they may also be worsened by physical activity, mental exertion, or sensory stimuli. In most cases, they may be reduced in amplitude but continue to occur during sleep. Depending on the underlying etiology of EPC and the amount of cortex involved, other seizure types and a variety neurologic deficits may be seen in these patients. Interestingly, EPC rarely includes additional symptoms, although sometimes EPC can evolve into complex partial seizures or secondarily generalized seizures [5, 12]. Thus, consciousness is maintained in the vast majority of cases of EPC although an ictal discharge can remain localized and still produce alteration of consciousness. Also, certain motor manifestations and a patient's anxious reaction to the symptoms may prevent the patient from appearing completely awake during seizures.

It may thus be difficult to ascertain the level of consciousness in some patients with EPC; a careful history and examination are helpful.

Outside of EPC, which presents with focal motor status epilepticus, the semiology of FSE depends on the area of cortex involved, as covered in more detail in other chapters.

Differential Diagnosis

Subcortical and segmental (i.e., spinal) myoclonus, tremor, and other extrapyramidal movement disorders and myoclonic epilepsy should all be considered in the differential diagnosis of EPC. Tremor has a characteristic alternating agonist–antagonist pattern, as opposed to the typically simultaneous activation of agonist and antagonist muscles in EPC [6]. Other extrapyramidal movement disorders such as dystonia, chorea, and hemiballismus, can also be mistaken for EPC. Subcortical and spinal myoclonus, present in a large variety of disorders, can also mimic EPC.

Sometimes, clinical observation alone will suffice to form a strong hypothesis. In examining the patient, one should describe the following: distribution (focal, multifocal, segmental, or generalized), temporal profile (continuous vs. intermittent, regular vs. irregular), and how EPC is activated (spontaneous, stimulus-induced, or induced by voluntary movement).

Often, ancillary neurophysiologic testing may be needed to distinguish among these disorders. These tests include EEG, EMG, SSEPs, jerk-locked back-averaging of EEG transients or SSEPs to EMG discharges, and long latency EMG responses to peripheral nerve stimulation [5, 25].

EEG Findings

The ability of scalp EEG to detect ictal activity during FSE depends on the size of the discharging cortical zone and the epileptic discharge's dipole orientation. Small epileptogenic foci may be missed entirely on ictal surface EEG recordings. Thus, in some cases, back-averaging can be used to detect time-locked EEG events preceding the EPC-associated myoclonic jerks [5]. Stereo-EEG or electrocorticography can also be helpful in localizing the underlying seizure focus.

In cases where scalp EEG does show abnormalities, there is no single pathognomonic finding that defines EPC. In one study of 32 cases, the most common EEG finding was regional spiking [3]. Other abnormalities included bursts of sharp waves or spike-and-wave discharges and unilateral or bilateral runs of abnormal rhythms [3]. In another study of 21 adults with EPC, the most common EEG finding was unilateral lateralized or localized spikes or sharp waves [26]. Other lateralized abnormalities seen were periodic lateralized epileptiform discharges (PLEDs, or LPDs), paroxysmal slow-wave activity, and lateralized continuous slow activity. Four patients had diffuse, continuous slow activity, and one had generalized periodic epileptiform discharges (GPEDs, or GPDs). In this study, only seven patients (33%) had epileptiform discharges during EPC that correlated with the myoclonic jerks.

Rarely, PLEDs/LPDs are observed time-locked to the myoclonic jerks of EPC. Thus, although PLEDs/LPDs are often considered an interictal phenomenon, there are clinical scenarios (such as EPC) in which they represent an ictal (i.e., epileptic seizure) pattern. The most common seizure type seen in the presence of PLEDs/LPDs is focal motor seizures affecting the contralateral body, often presenting as FSE or repetitive focal motor seizures [23].

In Rasmussen encephalitis, the severity of EEG abnormalities is often related to degree of clinical progression [8]. No specific EEG abnormalities are pathognomonic for Rasmussen encephalitis, but from an initially normal EEG, high-amplitude delta activity can develop over the affected hemisphere within months of seizure onset. Epileptiform activity and electrographic seizures are seen often, but EPC (as in other cases) is not always accompanied by recognizable ictal surface EEG changes [27, 28] (Fig. 11.1). Independent interictal abnormalities over the non-affected hemisphere emerge in 25% of patients within 6 months and in 62% of patients within 3–5 years of seizure onset. These contralateral abnormalities can be a marker of cognitive decline but do not appear to indicate bilateral disease per se [8].

Radiographic Findings

Neuroimaging techniques used to evaluate patients with FSE-EPC are evolving rapidly. Currently, 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. This is also true for cortically restricted abnormalities seen in mitochondrial diseases. In cases in which the suspected underlying pathology has caused breakdown in the blood–brain barrier (e.g., tumor, infection, active demyelinating lesion), MRI with gadolinium is also indicated.

It is important to note that the metabolic hyperactivity and changes in blood flow caused by seizures can induce transient, variably reversible changes on numerous MRI sequences (most notably on T2, FLAIR, DWI-ADC, and gadolinium-enhanced images) which may be widespread and lead to a broad, and potentially misleading, differential diagnosis [29].

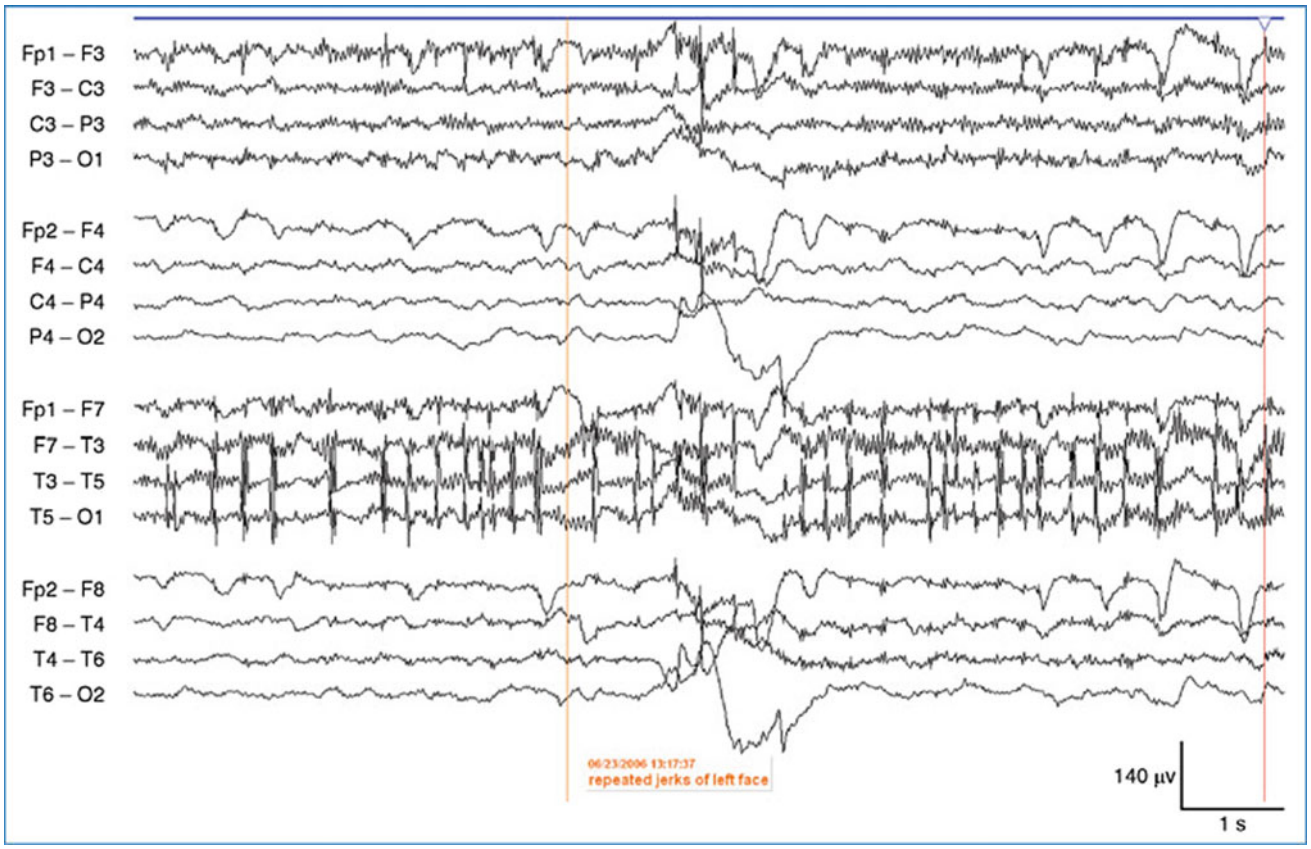

Fig. 11.1 Epilepsia partialis continua (*EPC*). Repeated myoclonic jerks of the *left face*, with muscle artifact on the left side of the EEG recording. Polymorphic delta slowing over the *right hemisphere,* predominant in the central region. Spikes are absent on this figure, which illustrates the poor clinical-EEG correlate of EPC. (From Korff and Nordli [28], with permission)

Dynamic imaging with 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 MRI is normal [22]. Because of the relative technical ease of obtaining a SPECT in patients having continuous focal seizures, this test can be particularly useful in the evaluation of EPC [30]. It can be used to clarify confusing situations when EPC is suspected but EEG fails to show epileptic changes.

Treatment and Prognosis

EPC is notoriously refractory to medical treatment [5]. As with all forms of epilepsy, it is essential to identify the underlying etiology and, when possible, treat appropriately for the underlying disease. For example, because nonketotic hyperglycemia and resultant hyponatremia are such frequent causes of EPC, it is crucial to obtain a complete metabolic panel and treat the underlying metabolic derangement. In patients with specific autoimmune diseases like Rasmussen encephalitis, treatment of the underlying disease process is key.

Anti-seizure drugs (ASDs) are the mainstay in the initial treatment of EPC, but their efficacy is usually limited and often, multiple ASDs are required to achieve a sustained effect [5]. In general, ASDs help to prevent the spread of EPC into complex partial or secondarily generalized seizures, but rarely do they appear to alter the severity of the EPC significantly. As in other types of SE, benzodiazepines are the most effective first-line drug for urgent interruption of EPC [31], but complete suppression often necessitates prohibitively high doses that may lead to marked sedation and respiratory depression.

There have been no large or randomized trials evaluating the efficacy of particular ASDs in the treatment of EPC. A retrospective, multicenter study of 65 cases of EPC (excluding patients with acute stroke or Rasmussen encephalitis as the etiology) found that topiramate and levetiracetam yielded a better overall success rate [31]. Topiramate was effective in 7 of 28 cases in which it was tried, and patients with a dysontogenetic etiology (four cortical dysplasias and one arteriovenous malformation) appeared to respond best. Levetiracetam was given to 26 patients and was successful in 8, five of whom had inflammatory etiologies. Other ASDs

including valproic acid and lacosamide have been reported as safe and effective in individual case reports, but in the absence of clinical trial data, we recommend that the choice of ASD be tailored to the individual case and side effect profile.

All patients presenting with FSE should be assessed carefully for an underlying lesion that may be amenable to curative resective surgery. Currently, the surgical literature for treatment of FSE is limited to case reports and case series. The majority of patients had EPC. The most common operations were focal resection, lobar or multilobar resections, hemispherectomy (functional, anatomical, or modified), and corpus callosotomy [24, 32]. Other surgical treatments have included multiple subpial transections, implantation of a vagus nerve stimulator, low-frequency repetitive cortical electrical stimulation, and thalamic deep brain stimulation [32–34].

A recent compilation of 23 case reports of the surgical treatment of FSE found that seizure freedom was achieved in 18 of the 23 patients, with follow-up periods of 4 months to 5 years [24]. A minority of patients had continuing but improved seizures at the time of reporting, without worsening of seizure frequency in any. Of note, the majority of the patients operated on were young (ages 8 days to 36 years), and had strong semiologic, imaging, or electrographic evidence (or combinations of these) of focal epilepsy, usually presenting with refractory status epilepticus on a background of habitual seizures. The great majority of patients had focal or hemispheric malformations of cortical development as the etiology.

One of the larger surgical case series included in the meta-analysis above involved 10 children with FSE refractory to high-dose ASDs who had various surgical treatments including callosotomy, lobectomy, or anatomic and functional hemispherectomy [31]. Their underlying illnesses included malformations of cortical development ($n = 6$), tuberous sclerosis ($n = 1$), Rasmussen encephalitis ($n = 1$), prenatal large-artery infarct ($n = 1$), and an unclear diagnosis ($n = 1$). In this study, SE was stopped by surgery in 100% of patients, with no perioperative mortality and with significant postoperative improvement in functional status.

Thus, based on the limited current literature, patients with convulsive or nonconvulsive refractory status epilepticus who have a high degree of concordance among semiology, imaging, functional imaging with PET/SPECT, and EEG (scalp as well as invasive) indicating a similar single epileptogenic zone (with focal cortical dysplasia as the underlying pathology) appear most likely to benefit from surgery. In patients with a nonlesional MRI or a poorly defined epileptogenic zone or both, invasive EEG monitoring should be considered strongly [24].

Unfortunately, the majority of patients with FSE are not candidates for surgery, for various reasons, e.g., when the expected motor deficit resulting from the removal of motor cortex is considered unacceptable, when the patient is otherwise neurologically normal, when EPC is bilateral, or when the case is nonlesional. A fascinating report describes a case of "mirror EPC," in which resection of a focal cortical dysplasia causing EPC resulted in the development of contralateral EPC in a previously undetected region of cortical dysplasia in the opposite hemisphere [35].

Fortunately, noninvasive techniques for the treatment of FSE are now being developed. A case report and case series found repetitive transcranial magnetic stimulation (rTMS) safe and potentially effective in the treatment of EPC [36, 37]. rTMS is a noninvasive method for focal cortical stimulation during which small intracranial electrical currents are generated repeatedly and applied by a strong fluctuating extracranial magnetic field. Interictal rTMS delivered over a neocortical seizure focus has been demonstrated to reduce seizure frequency in some patients, reducing cortical excitability via a yet unknown mechanism. Ictal rTMS is less well studied. The largest case series of ictal rTMS included seven patients with EPC of mixed etiologies. rTMS resulted in a brief (20–30 min) pause in seizures in three patients and a lasting (>1 day) pause in two more; the other two had no interruption in seizures [37]. Seizures were not exacerbated by rTMS in any patient, and side effects were generally mild (e.g., transient head or limb pain, or limb stiffening during high-frequency rTMS trains). Larger and more controlled studies are needed to explore the utility of rTMS in FSE, but at this time it is one of the only noninvasive, non-pharmacologic options for treatment.

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Myoclonic Status Epilepticus

12

Anna Serafini, Elizabeth E. Gerard, and Stephan U. Schuele

Definition

Myoclonus is characterized by sudden, brief, shock-like movements involving the extremities, face, and trunk, usually not associated with loss of consciousness [1]. Myoclonic seizures are triggered by epileptic activation of the motor cortex and typically associated with a short electromyogram (EMG) burst of 10–50 ms simultaneous activation of agonist and antagonist muscle activity, usually associated with an electroencephalography (EEG) correlate. Myoclonic status epilepticus (MSE) is an epileptic condition in which myoclonic seizures continue for more than 30 min.

Classification

Gastaut was the first to establish an etiologic classification of MSE distinguishing between "true" MSE seen in patients with epilepsy in contrast to acquired MSE as a symptom of another disorder [2]. True MSE is further divided into primary and secondary MSE (Table 12.1; Fig. 12.1) [3]. Juvenile myoclonic epilepsy (JME) is the prototype of a primary MSE. *Secondary* MSE is a term reserved for patients with a suspected symptomatic form of epilepsy, either generalized epilepsies such as myoclonic-astatic epilepsy (MAE), Lennox-Gastaut syndrome (LGS), Dravet Syndrome (DS), epilepsy with myoclonic absences, or a focal epilepsy presenting with *epilepsia partialis continua* (EPC).

According to Gastaut's classification system, acquired or *symptomatic* MSE is a term used for persistent myoclonic seizures in patients with no history of epilepsy, seen in the context of infectious, inflammatory, neurodegenerative, toxic-metabolic, or anoxic brain disease. MSE occurring in patients with progressive myoclonus epilepsies (PME) is classified among the symptomatic forms of MSE. For the purpose of this chapter, we will defer details on anoxic status epilepticus and "subtle" myoclonic status after generalized convulsions which are covered elsewhere in this book (see also Chap. 13, "Anoxic Myoclonic Status Epilepticus," and Chap. 17, "Treatment of Refractory and Super-Refractory Status Epilepticus").

Pathophysiology

Neuroanatomically, myoclonus can be classified into cortical, subcortical, spinal, and peripheral myoclonus. Epileptic myoclonus can be a cortical or thalamocortical phenomenon.

Cortical myoclonus is the consequence of an epileptic impulse that activates the sensorimotor cortex leading to myoclonic seizures. The neurons in the sensorimotor cortex may be the primary generator, or myoclonus can be driven by abnormal epileptic inputs propagating from other parts of the brain. Cortical myoclonus affects mainly the distal upper limbs and face. Cortical myoclonus often has multifocal generators, e.g., in patients with LGS or PME. It can have a single cortical generator, but the epileptic activation may spread through transcallosal or intrahemispheric cortico-cortical pathways, producing generalized or bilateral myoclonus [4]. Patients with focal or multifocal epileptic myoclonus may not have an EEG correlate on routine scalp recording. The neurophysiologic correlate of the myoclonus may only be detectable by using jerk-locked EEG or magnetoencephalograhy (MEG) averaging, or coherence analysis methods [5]. In jerk-locked back-averaging, EEGs spikes are averaged, time-locked with respect to the EMG onset to reduce the non–time-locked background EEG activities. A positive peak of the EEG spikes is expected to occur 15–20 ms prior to the myoclonus for the upper limbs, and 25–40 ms for the lower limbs. Spikes are located near the contralateral primary motor cortex. Cortical reflex myoclonus is considered a fragment of a focal or multifocal epilepsy

A. Serafini · E.E. Gerard · S.U. Schuele (✉)
Department of Neurology, Feinberg School of Medicine, Northwestern University, 710N Lake Shore Drive, Abbott Hall #1425, Chicago, IL 60611, USA
e-mail: s-schuele@northwestern.edu

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Table 12.1 Clinical and neurophysiologic characteristics of myoclonic status epilepticus (MSE)

Gastaut classification	Etiology	Exemplary condition	Mental status	EEG background	Typical duration of MSE	Clinical characteristics of myoclonus	Frequency of myoclonus	Stimulus-sensitive	EEG correlate	Time-locked EEG	Location of presumed physiologic disturbance
Primary MSE	Idiopathic generalized epilepsy	Juvenile myoclonic epilepsy	Alert	Normal	Hours	Synchronous Large amplitude Arms	Irregular Every few seconds, sometimes in clusters of 3–5 jerks	Some photosensitive	3–5 Hz generalized polyspike-wave	+	Thalamocortical
Secondary MSE	Symptomatic generalized epilepsy	Myoclonic-astatic epilepsy (of Doose)	Alert to stupor	Diffuse slowing, disorganized; slow spike-wave	Days to weeks	Asynchronous Fluctuating amplitude (small > large) Distal muscles	Irregular intervals Often nearly continuous	−/+	2–3 Hz generalized spike-wave or polyspike-wave complexes	+/−	Thalamocortical or cortical
		Dravet Syndrome (SMEI)	Stupor	Diffuse slowing, disorganized	Hours to days	Two forms: Isolated MSE—deltoid Obtundation status—face and limbs		−	Fast spike and wave	+	Cortical
	Symptomatic focal epilepsy	EPC	Alert	Regional slowing	Persistent, intractable	Unilateral, rhythmic, distal, arms	Regular, asynchronous, Around 1 Hz	+/− Somato-sensory	PLEDs/LPDs or no correlate	+ PLEDs (LPDs)	Cortical
Symptomatic MSE	Neurodegenerative	Progressive Myoclonic Epilepsies	Alert to lethargic	Background slowing; generalized spike-and-wave and focal spikes	Hours to days	Bilateral or multifocal Trunk, limb and facial muscles	Irregular intervals. Often nearly continuous, debilitating	+/− Photo-sensitive, startle, sound	Bilateral myoclonus with correlate. Multifocal jerks often without	+	Cortical
	Toxic-Metabolic	Renal failure	Lethargy to coma	Moderate background slowing	Variable	Asynchronous Variable amplitude	Irregular intervals	−/+	Multifocal spikes or slow spike-wave	+/−	Cortical and reticular
		Silver toxicity	Coma	Moderate slowing, then alpha coma	Variable	*	*	+/−	14–18-Hz electropositive central-frontal polyspikes	*	Cortical

Adapted from Gerard and Hirsch [3], with permission

EEG electroencephalography, *PLEDs* periodic epileptiform discharges, LPDs lateralized periodic discharges, *SMEI* severe myoclonic epilepsy in infancy, *EPC epilepsia partialis continua*

* detailed description not available

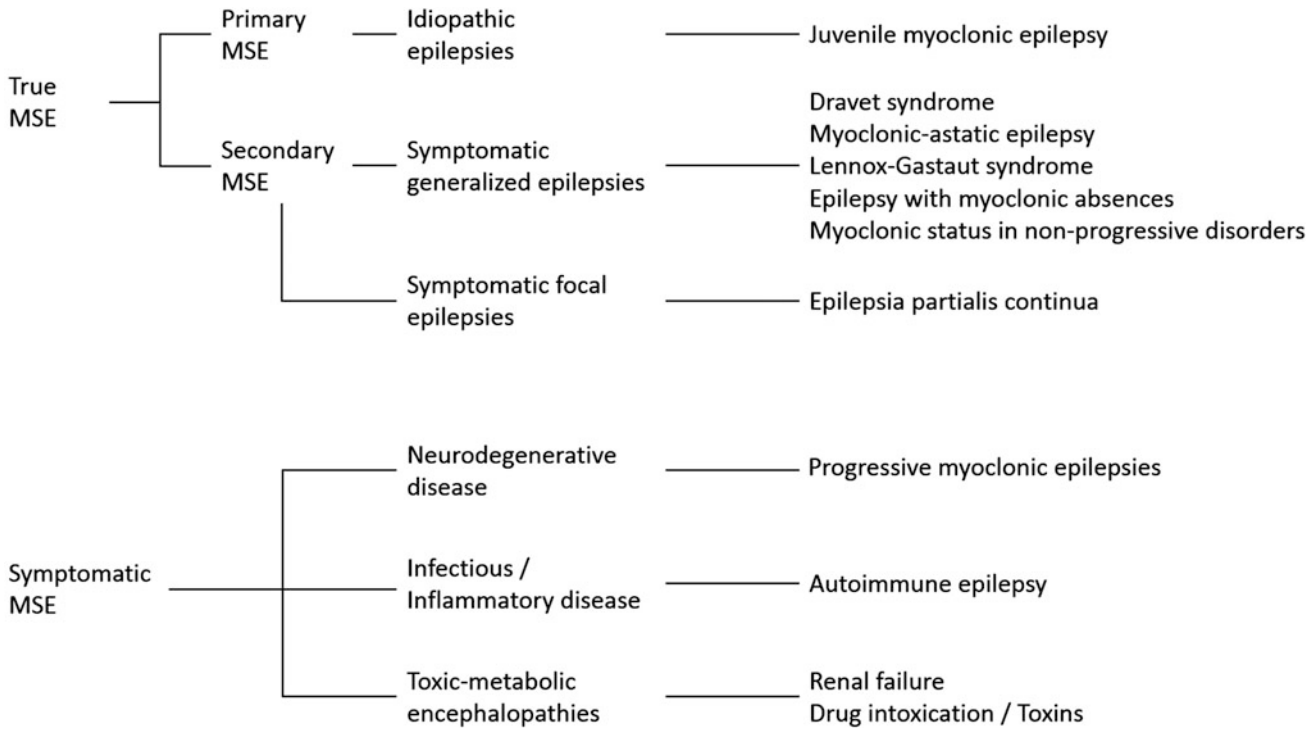

Fig. 12.1 Classification of myoclonic status epilepticus. Gastaut's proposed classification system divides myoclonic status epilepticus (MSE) into "true MSE", which occurs in patients with epilepsy, and "symptomatic MSE," which occurs as a result of another disease process. True MSE is further divided into primary and secondary forms of MSE. Adapted from Gerard and Hirsch [3], with permission

and involves a few adjacent muscles; it is often brought on by action or by sensory stimulation involving hyperexcitability of the sensorimotor cortex [1]. Cortical reflex myoclonus can be associated with giant somatosensory evoked potentials (SSEP) responses. For continuous muscle jerks from a focal cortical origin, the term *epilepsia partialis continua* (EPC) is used [6].

Myoclonic seizures associated with primary generalized epilepsies are considered a form of thalamocortical myoclonus which originates from ascending subcortical inputs that stimulate a hyperexcitable cortex diffusely and synchronously [6, 7]. Muscles are usually activated bilaterally. Muscles innervated by cranial nerves are activated rostrocaudally. Myoclonus is usually spontaneous, arrhythmic, and affecting mainly axial muscles. The myoclonus always has an EEG correlate of a generalized spike or polyspike-and-wave discharge. The negative peak of the generalized spike (which lasts 30–100 ms in duration) precedes the jerk (<100 ms duration) by 20–75 ms. Compared to cortical myoclonus, spikes are less strictly time-locked to the EMG jerk. Thalamocortical myoclonus is observed in JME, benign myoclonic epilepsy of infancy, and myoclonic-astatic epilepsy.

Reticular reflex myoclonus is seen in patients with metabolic abnormalities such as renal failure or anoxic brain injury and can be associated with cortical myoclonus. In those circumstances, the EEG shows generalized spikes, maximal over the vertex, usually not time-locked to the jerks. Giant SSEPs are not observed. Myoclonus can be spontaneous or stimulus-induced (although the temporal relationship to stimuli can be variable).

Negative myoclonus (NM) is characterized by a brief interruption of tonic muscular contraction for <500 ms, without evidence of preceding myoclonia [8]. NM is typically non-epileptic, e.g., the asterixis in hepatic encephalopathy. In specific conditions, the negative myoclonus can be associated with an epileptiform discharge and presents as epileptic negative myoclonus (ENM) [8–10]. Tassinari demonstrated that the onset of the EMG silent period was related to the negative component of the spike on the EEG, occurring before the slow wave [11]. ENM can be seen frequently in patients with the PMEs and in electrical status epilepticus during sleep (ESES syndrome) but is rarely considered a form of MSE.

Primary Myoclonic Status Epilepticus

Genetic Generalized Epilepsies

Genetic generalized epilepsies (GGE) are a subgroup of epilepsies with a presumed genetic etiology and usually without structural or anatomic abnormalities [12].

Based on associated seizure types, three forms of MSE can be distinguished in GGE patients:

- Type 1, also called "typical MSE" is seen in patients with bilateral myoclonic jerks synchronous with generalized polyspike-wave discharges on EEG and without impairment of consciousness [13, 14].
- Type 2 is defined by continuous myoclonic jerks preceded, followed, or interrupted by a generalized tonic–clonic seizure (GTCS). Consciousness is impaired in these patients during and after the GTCS but not during the buildup of myoclonic jerks preceding the convulsion.
- Type 3 is observed in patients with absence status with superimposed myoclonic jerks prominent in the eyelids, with variable involvement of the upper extremities. Consciousness is moderately impaired in these patients. A combination of types 2 and 3 can be observed and has been referred to as "atypical MSE".

The occurrence of MSE associated with GGE (or true primary MSE, according to Gastaut) is rare and seen mostly in JME [15]. JME is one of the most frequent types of GGE and is characterized by myoclonic seizures, tonic–clonic seizures, and absence seizures. The reported incidence is 3.2/1000 patient years [16]. In JME, the myoclonic jerks are bilateral, repetitive but arrhythmic, and predominantly involving the arms, sometimes trunk and legs, and rarely the face. Milder jerks produce more distal movements which can be asymmetric or focal based on report, direct observation or both. In MSE, the repetitive contractions and inhibitions produce a myoclonic tremor which can be disabling and interfere with ambulation. Consciousness is typically preserved. The myoclonus is invariably associated with an electrographic spike or polyspike-and-wave discharge (Fig. 12.2). In a study evaluating JME patients who were treated between 1994 and 1999, the authors found a prevalence of MSE of 1.4% [13]. A higher prevalence has been reported in studies based on patient reports without requiring EEG documentation [17, 18].

MSE in JME is frequently triggered by poor anti-seizure drug (ASD) compliance or inappropriate choice of ASD excessive alcohol intake, or sleep deprivation. MSE observed after inappropriate ASD use, is usually seen when narrow spectrum ASDs, such as carbamazepine, phenytoin, vigabatrin, or oxcarbazepine are used [14, 19]. This most commonly occurs when JME remains unrecognized or is mistaken for a focal epilepsy. Clinically, aside from the sometimes subtle and localized myoclonus, prominent asymmetric features in JME are seen in more than 10% of patients and described as lateralized myoclonic jerks or generalized convulsions preceded by a noticeable head version [20, 21]. Misinterpretation of EEG findings such as frontal or frontotemporal fragments of generalized discharges, asymmetric maxima of generalized epileptiform activity, or over interpretation of physiologic focal sharp transients may delay the diagnosis [22]. MSE in JME is typically easy to treat and resolves after the administration of a benzodiazepine (e.g., lorazepam or diazepam), valproic acid, or levetiracetam [23]. In cases caused by inappropriate ASDs, stopping the drug in question is paramount to prevent recurrence.

The pathophysiologic mechanism behind this drug-induced seizure aggravation is thought to involve the thalamocortical network, and in particular, the ventrobasal complex of the thalamus (VB), which enhances GABAergic action [24, 25]. Its activity is usually inhibited by the GABA-mediated activity of the reticular nucleus of the thalamus. Drugs such as oxcarbazepine or carbamazepine are presumed to enhance GABA-A transmission of the VB nucleus [26]. The increase in VB activity is not sufficiently opposed by the inhibitory action of the reticular nucleus, resulting in enhanced oscillatory thalamocortical activity, leading to more prominent and sustained sharp wave discharges [27]. Additionally, it has been demonstrated that ASDs that act mainly as voltage-dependent sodium channel blockers (such as carbamazepine and phenytoin) enhance membrane stabilization, leading to increased hypersynchronization of neuronal discharges. Lamotrigine, even though usually classified among the wider spectrum ASDs and effective against generalized seizures, may also worsen myoclonic seizures in some patients [26, 28].

Eyelid myoclonia (also known as Jeavons Syndrome) is a photosensitive epilepsy which starts in childhood and can persist into adulthood. Seizures consist of twitching of the eyelids, often associated with jerky upward deviation of the eyeballs and retropulsion of the head. Seizures can be frequent, often multiple in a day, and are usually triggered by eye closure in an illuminated room. The photosensitivity tends to decline with age. Eyelid myoclonic status, characterized by prolonged episodes of eyelid myoclonia, persisting at eye closure, has been described in a high percentage of patients (72%), more commonly during late childhood [29]. The ictal EEG is characterized by generalized polyspikes concomitant with the eyelid myoclonia.

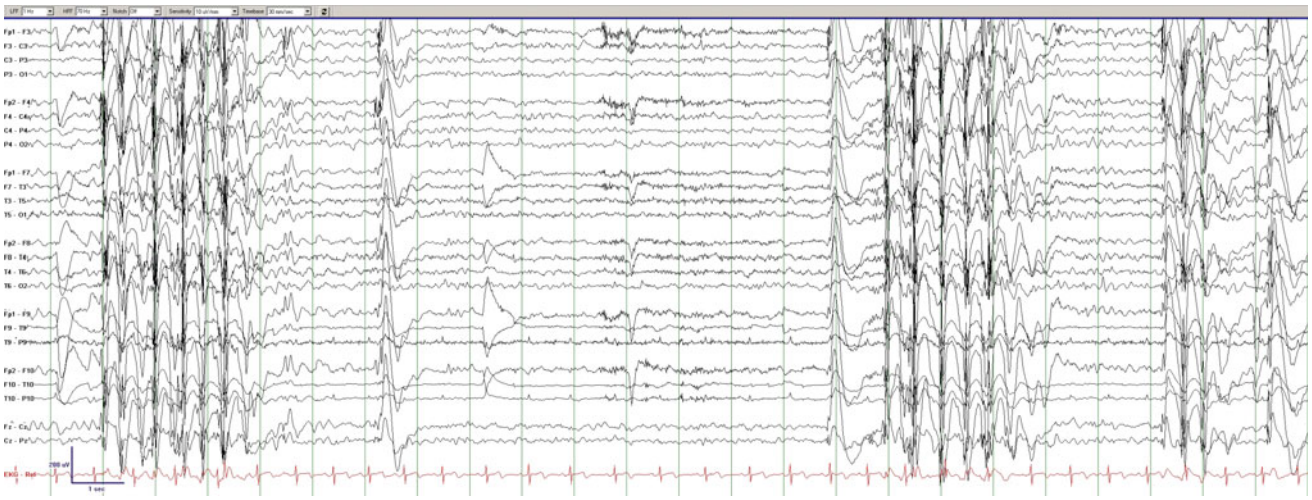

Fig. 12.2 Myoclonic status epilepticus in idiopathic generalized epilepsy. A 13-year-old girl with juvenile myoclonic epilepsy presented with frequent myoclonic jerks at age 12. Her mother also had myoclonus and seizures. She was unable to tolerate valproic acid due to weight gain and raised liver enzymes. On lamotrigine monotherapy she experienced an increase in the frequency and severity of morning myoclonus, which kept her from getting out of bed in the morning. During elective video-EEG monitoring, she had a cluster of myoclonic jerks recurring every 10–30 s for 40 min. Sample EEG demonstrates a drowsy background with frequent 3–4 Hz bifrontally predominant generalized polyspike-wave discharges. Myoclonic jerks involving the trunk, arms and legs occur in a sequence of 3–4 jerks with each polyspike-wave run lasting longer than 2 s. From Gerard and Hirsch [3], with permission

Secondary Myoclonic Status Epilepticus

Symptomatic Generalized Epilepsies

Dravet Syndrome. Dravet syndrome (DS), previously known as severe myoclonic epilepsy in infancy (SMEI), is an epileptic encephalopathy that typically presents with prolonged febrile seizures in the first year of life followed by a variable course that includes different seizure types, developmental regression, and seizure intractability [30]. Most cases result from a de novo mutation of the SCN1A gene, which encodes the voltage-gated sodium channel Nav1.1 [31]. Myoclonic jerks are divided into myoclonic seizures and non-epileptic myoclonus based on the presence of an epileptiform EEG correlate [32]. Myoclonic seizures can be dramatic in DS, involving the axial muscles, often causing the child to fall. The massive jerks are frequently mixed with numerous asynchronous and arrhythmic distal myoclonic jerks, often without a clear epileptiform EEG correlate and difficult to differentiate polygraphically from non-epileptic myoclonus.

The occurrence of MSE in DS is rare; this group of patients usually presents with convulsive status epilepticus, which can occur in up to 75% of patients within the first years [33, 34]. Yakoub and colleagues reported the occurrence of MSE in 3 out of 17 patients with a diagnosis of DS [35]. In these 3 patients MSE lasted, respectively, 3, 24, and 36 h and occurred at the ages of 14 months, and 4 and 5 years. The EEG correlate of MSE was characterized by rapid high voltage arrhythmic generalized fast spike waves (3–5 Hz) accompanied by myoclonic jerks (mostly in deltoid muscles), at times associated with tonic contractions.

Patients with DS often present with "obtundation status" which can occur in up to 40% of patients and consists of fluctuating alteration of consciousness with slight increased postural tone and fragmentary and segmental, erratic myoclonus of low amplitude, involving the limbs and the face [33, 36]. It can last for several hours or even several days and it can be interrupted by strong sensory stimuli. The EEG is characterized by diffuse slow waves intermixed with focal and diffuse spikes, sharp waves, and spike and waves, of higher voltage over the anterior regions and the vertex without correspondence between the spikes and the myoclonic jerks. Even though myoclonic jerks seem to be frequent in this clinical manifestation, given the absence of a true relationship between the myoclonus and the spikes, it is usually not classified as a MSE but as a form of atypical absence status.

Lennox-Gastaut Syndrome. Lennox-Gastaut syndrome (LGS) is a severe childhood epileptic encephalopathy characterized by frequent seizures, progressive cognitive impairment, drug resistance, and typically a characteristic EEG pattern with slow spike and slow wave pattern and runs of polyspikes during sleep. Different seizure types may coexist: tonic seizures, atypical absence, GTC, and myoclonic seizures. Myoclonus in LGS is seen in 10–30% of patients and can range from brief jerks of the face and head to massive bilateral myoclonus and falls, arising spontaneously. Consciousness is usually intact unless the seizures cluster. The myoclonic seizures are associated with brief bursts of 3–

3.5 Hz generalized spike or spike-and-wave activity. At least one or more episodes of status epilepticus have been reported in most patients (about 90%) [37]. The most frequent form of status epilepticus is absence status. MSE is extremely rare in this group of patients and if present is suggestive of a diagnosis of MAE. One case report of MSE in LGS described MSE due to lamotrigine treatment [38, 39].

Myoclonic-Astatic Epilepsy (of Doose). Myoclonic-astatic epilepsy (MAE) is a generalized epilepsy syndrome characterized by different seizure types (myoclonic, myoclonic-astatic, and generalized tonic–clonic seizures), typically with onset between 7 months and 6 years of age. In contrast to LGS, MAE initially presents with a normal development and has often a more benign course, with at least half of the patients entering remission. In the majority of patients, febrile and nonfebrile tonic–clonic seizures precede the onset of the myoclonic and myoclonic-astatic seizures [40, 41]. Thirty-six percent of patients develop status epilepticus, with features of atypical absences and myoclonus lasting hours or even a few days [39, 42]. The episodes of MSE are described as loss of contact, alteration of vigilance, drooling, speech disorders, and erratic myoclonus. The myoclonus is predominantly seen in the face, extremities of upper limbs, eyelids, mouth, tongue, and finger. The EEG is characterized by 2–3 Hz spike-and-wave activity, and irregular polymorphous hypersynchronous activity (Fig. 12.3).

MSE tends to occur in MAE patients with unfavorable outcome and accelerated mental deterioration. As described for JME, cases of MSE in MAE can be triggered by ASDs, specifically carbamazepine, vigabatrin, and levetiracetam [6, 40, 43]. Treatment consists of benzodiazepines and valproate or ethosuximide. Patients usually respond to treatment, but MSE may recur.

Epilepsy With Myoclonic Absences. Epilepsy with myoclonic absences was first described by Tassinari and colleagues in 1969 [44]. The syndrome is rare, with onset between 2 and 12 years of age, more frequently seen in boys and characterized by absence seizures associated with rhythmic myoclonic jerks, and in about half the patients, GTCs as well. The EEG shows bilateral synchronous and symmetric 3 Hz spike-and-wave discharges. In Tassinaris's case series, only 1 patient out of 36 presented with MSE, which was interrupted after the administration of IV diazepam.

Myoclonic Status in Non-Progressive Encephalopathies. Myoclonic status in non-progressive encephalopathies (MSNE) was first described in 1980 by Dalla Bernardina and colleagues after observing seven children with cerebral palsy due to severe prenatal or neonatal cerebral damage, presenting with recurrent long-lasting myoclonic status [36]. The same electroclinical picture was later described by others [45, 46]. Based on electroclinical characteristics, three types of MSNE can be identified:

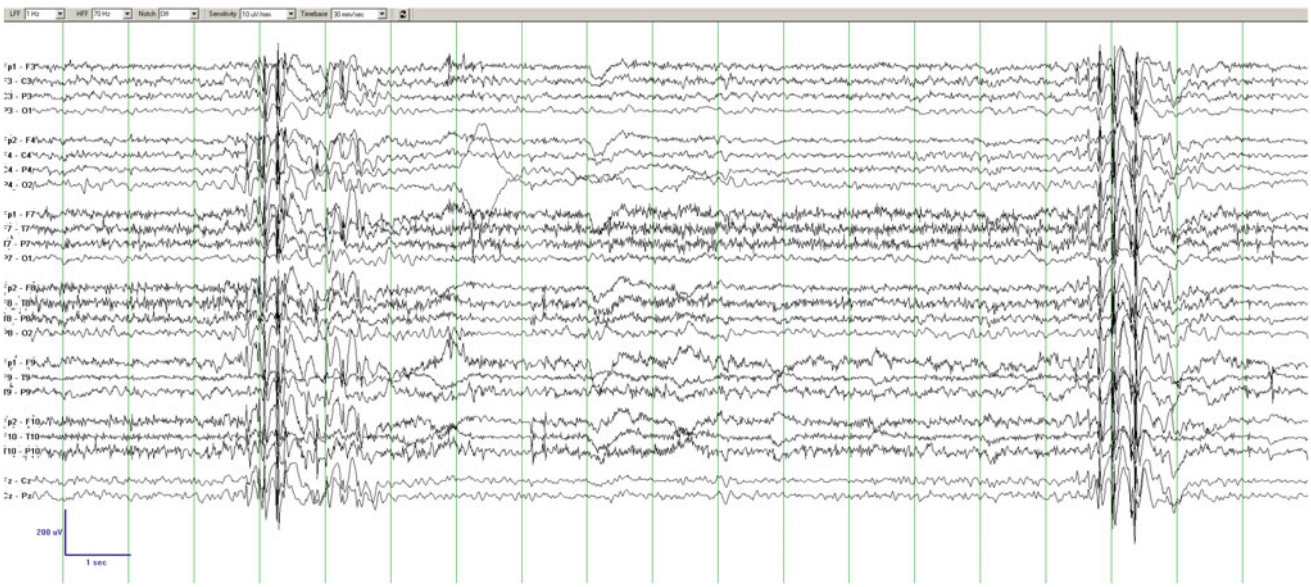

Fig. 12.3 Myoclonic status epilepticus in myoclonic-astatic epilepsy. A 65-year-old woman had mild mental retardation and myoclonic-astatic epilepsy since childhood. Seizures had been infrequent for many years. In the setting of withdrawing levetiracetam she developed frequent myoclonic jerks characterized by sudden flexion of her trunk and neck with elevation and extension of both her arms. At their most frequent, these jerks occurred twice a minute for 15 min. The patient was able to talk and interact with examiners between jerks. The EEG background shows mild diffuse slowing with a 10 Hz alpha rhythm and frequent 4–5 Hz bifrontally predominant polyspike-wave discharges corresponding to the myoclonus. Myoclonic jerks continued frequently (10–25/h) for 24 h. This improved dramatically with reinstitution of levetiracetam. From Gerard and Hirsch [3], with permission

The first group is characterized by absences associated with almost continuous jerks (rhythmic or arrhythmic) and positive brief myoclonic absences and hypnagogic startles. This subgroup includes: Angelman syndrome (AS), Prader–Willi syndrome, and Rett syndrome [47, 48]. No neuroradiologic abnormalities are usually observed. The EEG is characterized by high amplitude slow waves with superimposed spikes involving the posterior regions, associated with rhythmic myoclonias observed on the EMG record. Subcontinuous delta-theta activity involving the central areas is seen, as well. These patients are usually refractory to treatment; benzodiazepines and ACTH generally have a transitory effect. Improvements have been observed with ethosuximide, associated with valproic acid treatment, or levetiracetam [47].

The second subgroup is characterized by the association of absence status and a negative, continuous, and semirhythmic myoclonus, mixed with sudden uncontrolled continuous dyskinetic movements, leading to a clinical picture of hyperkinetic loss of posture [48]. Patients are typically females with developmental cortical malformations. The EEG is characterized by continuous slow spike-wave associated with continuous rhythmic jerks with long-lasting inhibitory phenomena or alternating bilateral positive myoclonic jerks and prolonged negative myoclonus. These seizures are usually refractory to treatment.

The third group is characterized clinically by rhythmic myoclonia of the face and limbs. As the disease progresses, the clinical picture worsens with the appearance of pyramidal tract signs and intention tremors, as well as myoclonus followed by muscle inhibition. This subgroup is characterized mainly by progressive neuromuscular deterioration. A frequent finding in these patients is cortical dysplasia involving the motor area. The EEG is characterized by continuous spike activity in the rolandic region, accompanied by bilateral rhythmic myoclonia followed by prominent periods of inhibition. The EEG shows a subcontinuous series of generalized spike-wave type paroxysms, or bilateral continuous slow wave with notched delta appearance with corresponding rhythmic myoclonia of the face and limbs. This activity changes with time, and the paroxysms become sharp theta waves with very slow semirhythmic continuous spikes over the central regions and vertex.

These cases of subtle myoclonic status can go unrecognized clinically because of the mental retardation and concomitant continuous abnormal movements. Polygraphic recordings with EMG leads are very useful for recognizing these syndromes. Early recognition is important in order to start adequate treatment with the hope of preventing neuropsychologic deterioration.

Symptomatic Focal Epilepsy

Epilepsia Partialis Continua. *Epilepsia partialis continua* (EPC) has been defined as irregular myoclonic or regular clonic muscle twitches affecting a limited part of the body, occurring for a minimum of one hour, and recurring at intervals of no more than 10 s [49]. The underlying etiology is variable, from static insults to progressive disorders such as Rasmussen's syndrome or other forms of autoimmune epilepsy, vasculitis, nonketotic hyperglycemia, or encephalitis.

The jerks are typically highly variable in duration, rate, intensity, and distribution and can be rhythmic and arrhythmic, typically spontaneous but also triggered by somatosensory stimulation. The clonic or myoclonic seizures are often associated with other seizure types. The EEG typically shows repetitive spikes or periodic lateralized epileptiform discharges (PLEDs), although the relationship to the jerk can be complex, and the absence of EEG findings does not exclude the diagnosis (Fig. 12.4). Based on jerk duration, EMG is helpful in distinguishing cortical vs subcortical types of myoclonic jerks. Cortical myoclonic jerks usually last <100 ms, and subcortical-based myoclonic jerks > 100 ms. The muscle jerks involve agonistic and antagonistic muscles simultaneously [50, 51].

Treatment of EPC depends on the underlying cause. Levetiracetam, valproate, and benzodiazepines are commonly used ASDs. Despite medications, the continued focal jerking in EPC is often refractory to ASDs, which nevertheless are indicated to prevent secondarily generalized seizures [52]. When EPC is seen in autoimmune forms, high dose steroids, intravenous immunoglobulin (IVIG), and plasma exchange are used. Surgery is a therapeutic option when focal lesions are the cause of EPC. If the epileptogenic region involves the primary motor cortex, multiple subpial transection is a possibility [51]. Functional hemispherectomy is indicated for Rasmussen patients with progressive deterioration unresponsive to immunotherapy. Transcranial magnetic stimulation has been tried in patients with refractory EPC [53].

Symptomatic Myoclonic Status Epilepticus

Frequent, persistent myoclonic jerks can be seen in a variety of non-epileptic causes of myoclonus including neurodegenerative disorders such as Alzheimer disease, movement disorders including Huntington disease or Wilson disease, disorders such as Creutzfeldt-Jakob disease (CJD) or subacute sclerosing panencephalitis (SSPE), or associated with

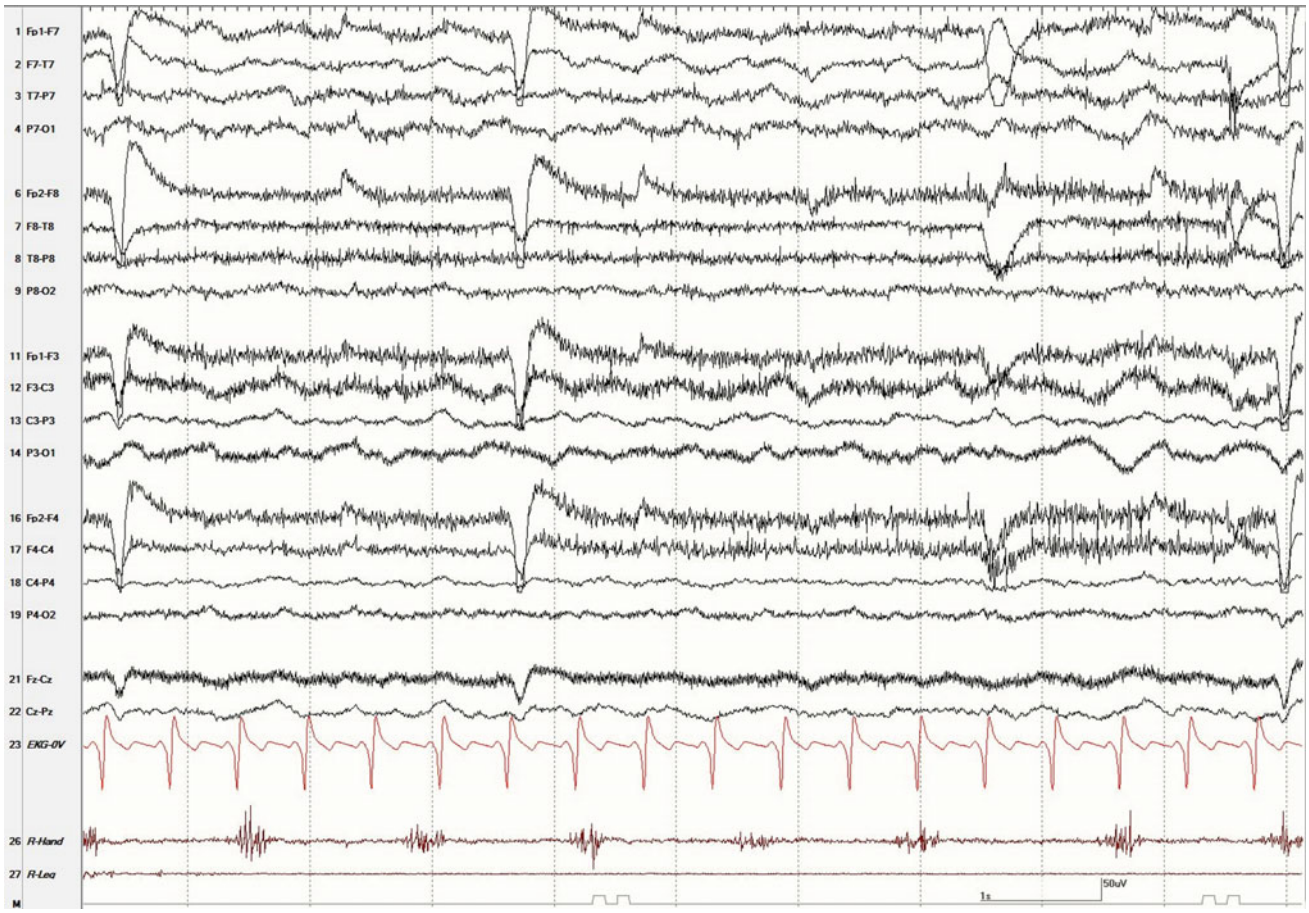

Fig. 12.4 *Epilepsia partialis continua* (EPC). A 28-year-old right-handed woman presented with confusion, speech difficulty, and right arm numbness. During admission she started presenting right hand middle finger twitching. Continuous video-EEG monitoring showed continuous focal slowing over the left hemisphere. No interictal epileptiform discharges were seen. Electromyogram leads were placed on the right hand and demonstrated rhythmic clonic and myoclonic activity of 1 Hz, consistent with *epilepsia partialis continua.* The patient's cerebral imaging was normal. Autoimmune work-up on serum and cerebrospinal fluid showed NMDA and serum N-type calcium channel antibodies

toxic-metabolic encephalopathies. Certain conditions, such as CJD or SSPE and some forms of metabolic encephalopathies, can show periodic discharges associated with the myoclonus.

Myoclonus has been observed in 50–100% of patients with CJD, particularly in advanced stages of the disease [54]. At the onset of disease, myoclonus is sporadic and spontaneous. With progression, myoclonus spreads to the whole body. Periodic positive myoclonus is observed most frequently, recurring every 0.5–2 s; it is observed at rest and during active movements. The EMG bursts are usually time-locked, with periodic sharp wave complexes (PSWCs) that are not considered an epileptic cortical activation but rather related to a hyperkinetic motor facilitation [55].

Neurodegenerative Disorders

Progressive Myoclonus Epilepsies. The progressive myoclonus epilepsies (PME) are a group of epilepsy syndromes characterized by myoclonic jerks, generalized seizures, mental retardation, and ataxia [56]. These syndromes are extremely rare and represent <1% of people with epilepsy seen at specialist centers. They are hereditary neurodegenerative diseases, including neuronal ceroid lipofuscinosis (NCL), dentatorubral—pallidoluysian atrophy (DRPLA), Gaucher disease, mitochondrial encephalopathy with ragged red fibers (MERRF), Lafora disease, and Unverricht-Lundborg disease (ULD). Epilepsy results from pathologic processes specific to each entity, such as an accumulation of

neurotoxic materials at specific layers in the cerebral cortex [57]. Myoclonus in PME is typically fragmentary and multifocal, and is often precipitated by posture, action, or external stimuli such as light, sound, or touch. It is particularly apparent in musculature of the face and distal extremities. Bilateral massive myoclonic jerks that tend to involve muscles of proximal limbs may also occur. Negative myoclonus is often seen as well. In Unverricht–Lundborg disease, there is marked photosensitivity. Back-averaging techniques have demonstrated how EEG spikes usually precede the myoclonic jerks in these patients. Additionally, giant SSEPs are often seen, suggesting that the myoclonic jerks in PME have a cortical origin. During the early phase of these disorders, seizures are usually responsive to ASDs. As the disease progresses, the myoclonus gradually becomes refractory to medication and episodes of MSE can be seen (Fig. 12.5).

In a study reviewing the natural history of nine patients with PME, epilepsy gradually became refractory, and status epilepticus emerged 3–19 years after the onset of epilepsy in all nine patients [58]. "Symptomatic" MSE was seen in seven patients of the nine patients. The remaining two had generalized tonic–clonic status. Based on clinical manifestations, the majority had generalized myoclonus. Only one patient had multifocal myoclonic jerks of the face, limbs, and trunk during wakefulness. The authors noted that certain types of PME had a propensity to develop a certain type of status epilepticus: MSE was common in late-infantile type NCL, and generalized convulsive status epilepticus was common to DRPLA, although these findings have not yet been confirmed by other studies [58].

Treatment of MSE for these patients is similar to that for other forms of MSE, including intravenous benzodiazepines (diazepam, lorazepam, clonazepam, and midazolam), valproate, and levetiracetam [59]. In PME patients, phenytoin and fosphenytoin should be used with caution because of their potentially aggravating effect on the neurologic symptoms and the risk of cerebellar degeneration [60]. There are, however, reports of good responses to phenytoin [58]. Sodium channel blockers and GABAergic drugs (tiagabine, vigabatrin) as well as gabapentin and pregabalin should also be avoided, as they may aggravate myoclonus and myoclonic seizures. Myoclonic jerks in PME are often stimulus-induced, and patients with MSE should avoid loud noises and bright lights. In PME associated with mitochondrial disease, valproate and other ASDs that may interfere with mitochondrial function, should be avoided.

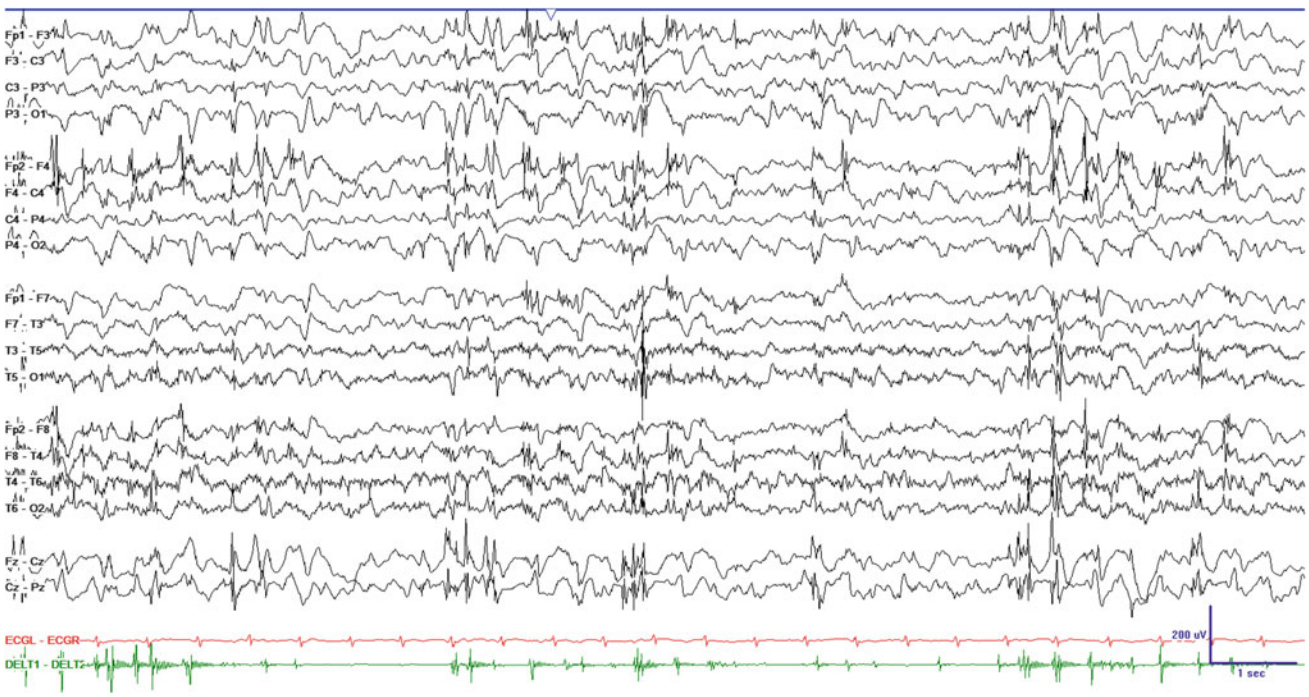

Fig. 12.5 Myoclonic status epilepticus in progressive myoclonic epilepsy. A 16-year-old had a progressive myoclonic epilepsy, the cause of which was unknown despite extensive testing of blood, urine, and cerebrospinal fluid (CSF), including whole exome sequencing, mitochondrial genetic testing, and muscle biopsy. Her clinical course suggested a mitochondrial disorder, with a mildly elevated CSF lactate, raised liver enzymes after one IV load of valproate, and the development of weakness, peripheral neuropathy, and ophthalmoplegia. The patient was living at home and had chronic and frequent myoclonic jerks. She was treated with clobazam, levetiracetam, primidone, and zonisamide. Image courtesy of Alexandra Shaw, MD, Lurie Children's Hospital of Chicago, Northwestern University Feinberg School of Medicine, Chicago, Illinois, USA

Toxic-Metabolic

Drug-Induced Myoclonic Status Epilepticus. Medication-induced MSE can occur in patients with and without epilepsy. As previously described, in patients with GGE the use of narrow spectrum ASDs (such as carbamazepine, phenytoin, and oxcarbazepine) puts them at risk of developing MSE. In patients without epilepsy, a different set of medications can provoke *de novo* MSE (Table 12.2). Among patients without a history of epilepsy, pregabalin and tiagabine have been associated with MSE [61, 62]. Clinically, patients present with continuous irregular generalized myoclonic jerking (mainly affecting the upper limbs) associated with normal or only mild impairment of consciousness. The EEG shows generalized polyspike-and-wave complexes which normalize after the (inappropriate) medication is discontinued and lorazepam is given. Patients who develop MSE following treatment with pregabalin usually have impaired renal function, mild to moderate cognitive impairment, or both [61]. Cases of MSE have been reported with doses of pregabalin from 150 to 300 mg /day. Dose dependency was only observed in animal models—where higher doses of pregabalin were associated with increased spike-wave activity in a dose dependent manner [63]. The pathogenesis of the myoclonus is still unclear. It has been suggested that high doses of tiagabine (120 mg/day) cause an inversion of the GABAergic effect from inhibitory to excitatory due to excessive stimulation [62].

Cephalosporin-type antibiotics such as cefepime and other antibiotic such as carbapenem have also been associated with a neurotoxic syndrome with encephalopathy with generalized periodic discharges with an atypical triphasic morphology and non-rhythmic, stimulus-sensitive myoclonus. This is most commonly seen in patients with renal impairment but can also occur in patients with normal renal function. The main mechanism of neurotoxicity appears to involve GABA-A receptor inhibition, although other mechanisms are possible [64]. Whether, or at what point, the rhythmic triphasic waves represent a form of status epilepticus is still disputed given the absence of other associated seizure types and lack of a clear evolution and offset of the abnormal electrographic activity.

Renal Failure. Myoclonus in the setting of uremia is common, often consisting of action-related myoclonus. The etiology is usually related to the underlying metabolic encephalopathy. The EEG shows diffuse slowing, with or without triphasic waves. The condition improves with dialysis and kidney transplantation. In rare cases, myoclonic seizures or even MSE can be seen (Fig. 12.6). In those cases, the myoclonus presents with short, irregular, spontaneous multifocal jerks which can involve the face. The EEG demonstrates central or generalized spikes which may or may not be time-locked with the myoclonic seizures.

Epileptic myoclonus can also be observed in the setting of renal failure in specific syndromes. Action myoclonus-renal failure is a specific autosomal recessive syndrome of action myoclonus observed in renal failure. This syndrome independently affects the kidney, with focal glomerulosclerosis causing renal failure and progressive myoclonus epilepsy (PME) or progressive myoclonic ataxia (PMA) [65]. Onset is usually in the late teens or early twenties. Neurologic manifestations can precede the renal involvement in a third of cases. If the neurologic symptoms precede the renal failure, it can be challenging to make the correct diagnosis. Patients can present with tremor at rest as the only clinical symptom. In these cases, a correct diagnosis

Table 12.2 Iatrogenic and toxic causes of myoclonic status epilepticus

	In patients with epilepsy	In patients with or without epilepsy
Anti-seizure drugs	Carbamazepine Gabapentin Lamotrigine Oxcarbazepine Phenytoin Pregabalin Tiagabine Vigabatrin	Pregabalin Tiagabine
Other drugs/toxins	Duloxetine Paroxetine	Cefepime Olanzapine Lithium (overdose) Penicillin Radiocontrast (intrathecal) Colloidal silver Aluminum (dialysis syndrome) Other heavy metals

Drugs and toxins that have been reported to provoke myoclonic status epilepticus in patients with history of generalized epilepsy, or cause symptomatic myoclonic status epilepticus in patients without a history of epilepsy, or both

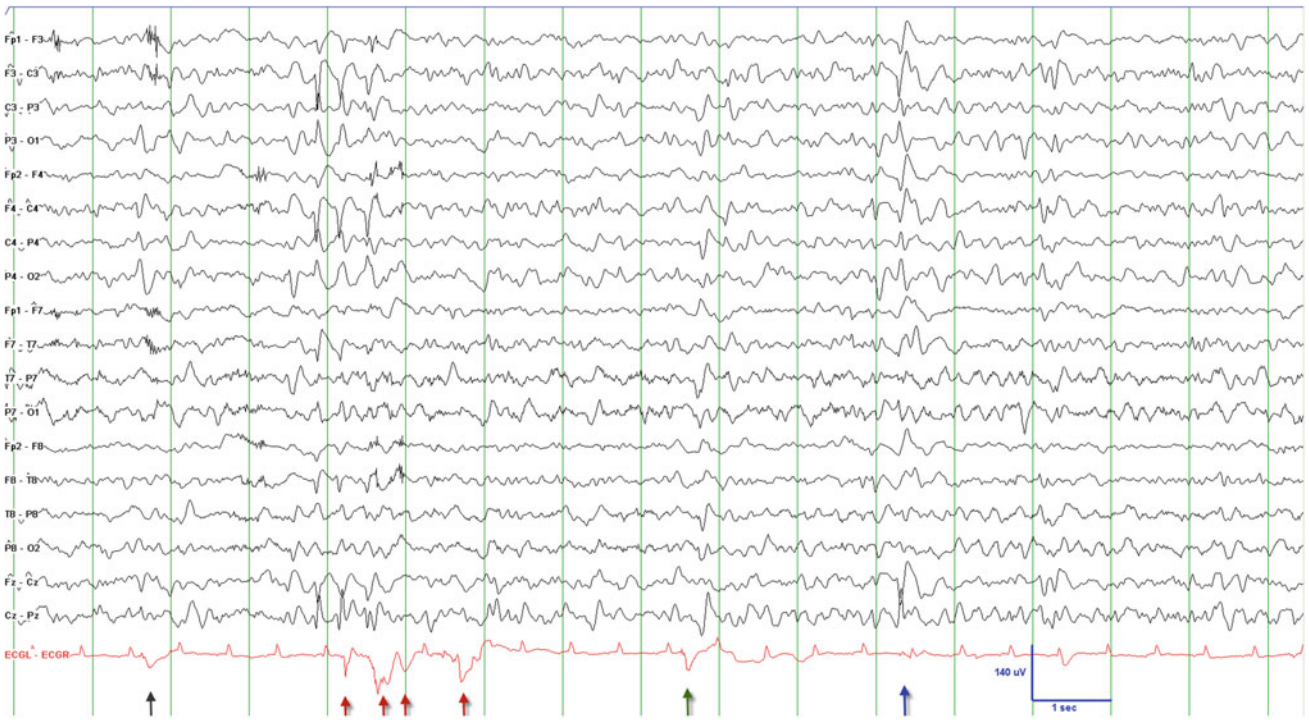

Fig. 12.6 Myoclonic status epilepticus in the setting of renal failure. A 65-year-old man had a history of bilateral kidney transplantation complicated by autoimmune rejection. He presented on two occasions with decreased mental status and frequent myoclonic jerks over a period of more than 24 h in the setting of acute on chronic renal failure. On exam, he had both synchronous and asynchronous myoclonic jerks predominantly affecting the upper extremities. Video-EEG demonstrated moderate diffuse background slowing and frequent central sharp waves. Movement artifact in the EEG lead corresponds to myoclonic jerks of right shoulder (*black arrow),* left arm and shoulder (*red arrows*), torso (*green arrow*) and head (*blue arrow*). Some of the myoclonic jerks immediately follow a central sharp wave (*first three arrows*), but others do not have a clear EEG correlate (*second three arrows*). The patient's myoclonus and mental status improved following dialysis. From Gerard and Hirsch [3], with permission

is often made only when more progressive symptoms of myoclonus appear. Involuntary, action-activated myoclonic jerks that involve bulbar, proximal, and distal limb muscles are observed, as well as involuntary spontaneous myoclonic jerks and generalized clonic–tonic–clonic seizures. The diagnosis is confirmed in individuals with bi-allelic (homozygous or compound heterozygous) loss-of-function pathogenic variants in SCARB [66]. The EEG may demonstrate spike and spike-wave complexes. Autopsy shows extraneuronal lipofuscin accumulation in the brain. The prognosis is usually poor; renal transplantation is often necessary [67]. Galloway-Mowat syndrome is an autosomal recessive disorder in which microcephaly and cerebellar ataxia are observed in children with focal segmental glomerulosclerosis and proteinuria. Frequent focal myoclonic and atonic seizures are seen [68].

Silver Toxicity. Silver toxicity has long been known to cause seizures [69, 70]. Recently, silver toxicity has been documented as a cause of MSE [71]. This case report detailed the development of MSE after ingestion of a colloidal silver drink, in which the MSE became refractory to various doses of lorazepam, midazolam, clonazepam, valproate, phenytoin, phenobarbital, and propofol [71]. The EEG showed 14–18 Hz electropositive centro-frontal spikes and polyspikes during myoclonic jerks. Patients who develop MSE due to silver toxicity seem to be refractory to treatment because of the potential irreversible neurologic toxicity. The reason that silver accumulation causes seizures is not well known. It has been suggested that silver affects membrane permeability of neuronal cell bodies (due to its effect on the lipid peroxidation of the neuronal cell membrane) and increases the release of intracellular calcium, leading to increased neuronal excitability [72]. Even though chelation therapy is effective in removing large amounts of silver, the brain seems to retain silver, particularly in the cortex [71].

Inflammatory

Autoimmune Myoclonic Status Epilepticus. Non-epileptic myoclonus can be seen in a variety of autoimmune syndromes. Opsoclonus-myoclonus-ataxia syndrome is an autoimmune disorder characterized by chaotic myoclonic

ocular movements, ataxia, and myoclonic activity. It occurs in adults and in children. When occurring in children, it is part of a paraneoplastic syndrome due to either a neuroblastoma or a ganglioneuroblastoma [73, 74].

Rasmussen syndrome is a progressive epileptic encephalopathy often presenting with focal MSE and associated with anti-Ri (also known as ANNA-3) antibodies. An underlying autoimmune, T-cell mediated mechanism is thought to be responsible. Rasmussen syndrome, an autoimmune disorder, is often medically intractable, despite treatment with steroids, IVIg, or plasmapherisis. Hemispherectomy is often required for controlling epilepsy and preventing involvement of the contralateral hemisphere. EPC with myoclonic facial twitching and arm jerking, is the most commonly described semiology in paraneoplastic epilepsy with anti-Hu antibodies [75, 76]. Focal MSE has also been described in patients with NMDA encephalitis [77].

Diagnostic Work-up of Myoclonic Status Epilepticus

When a patient presents with MSE, the first step is to obtain a detailed history. The patient's age, ethnicity, prior history of epilepsy, and recent history of anoxic injury, are all important for distinguishing among the different forms of MSE. The second step in the differential diagnosis is obtaining basic metabolic laboratory tests, including urine and serum toxicology, and a heavy metal screen. If CJD suspected, cerebrospinal fluid (CSF) can be sent for protein 14-3-3. High resolution MRI is crucial for secondary and suspected symptomatic MSE.

EEG is often useful in confirming the epileptic etiology of the myoclonus and to distinguish among the different types of MSE and underlying epilepsy syndromes. In complicated cases, it can be helpful to use neurophysiologic studies such as jerk-locked back-averaging with simultaneous EEG and EMG, somatosensory evoked potentials (SSEPs), and long-latency EMG responses in order to define the neuroanatomic origin of myoclonus. These tests can also help to identify psychogenic myoclonus. Large amplitude "giant" SSEPs, are a reflection of cortical hyperexcitability and are typically seen with most PMEs but are also present in other forms of cortical myoclonus such as Alzheimer disease.

The PMEs represent a very rare group of epileptic syndromes. Only a minority of patients present with MSE. MSE is usually seen at later stages of the disease, once the diagnosis has been established, but PMEs may be hard to diagnose at the onset, as the clinical features may mimic those in GGEs. In contrast to GGE patients, PME patients show poor response to therapy and worsening of the myoclonic seizures over time. As the disease advances, progressive neurologic symptoms such as ataxia and dementia become apparent. Over years, the EEG shows progressive changes: the background becomes slow and, toward the end of the disease, highly disorganized. Epileptiform discharges (mostly characterized by high voltage spike or polyspike-and-wave discharges) become almost continuous. A full history of the illness, age of onset, progression, developmental history in children, family history suggestive of PME, and thorough clinical examination are crucial to obtain the diagnosis, which may then warrant further genetic testing. The mode of inheritance, especially if dominant, can help to distinguish among various forms of PME: most PMEs are autosomal recessive disorders, except for adult NCL (Kufs disease) and DRPLA (which are autosomal-dominant) and MERRF, which shows a maternal inheritance. Molecular genetics are necessary to identify the specific type of PME.

Neurophysiologic studies can show distinguishing features. Background slowing and disorganization are particularly evident in PME forms with relentlessly progressive dementia, such as Lafora disease and NCL. Most PMEs show generalized epileptiform abnormalities such as fast spike-and-wave, multiple spike-and-wave, or multiple spike discharges. Focal occipital spikes are common in Lafora disease. Other more specific findings are vertex spikes dominant epileptiform abnormality in sialidosis; activation of epileptiform abnormalities in non-REM sleep in the sialidoses and the late-infantile and juvenile forms of NCL; photosensitivity to single flashes in late-infantile and adult NCL; and absent electroretinogram (ERG) in late-infantile and juvenile NCL. SSEPs frequently show giant responses. Skin biopsy looking for Lafora bodies (acid-Schiff positive intracellular polyglucosan inclusion bodies) is indicated when Lafora disease is suspected. In patients in whom MERFF is suspected, muscle biopsy is appropriate, looking for ragged red fibers. Fundoscopy is helpful in the diagnostic process, as visual and ophthalmologic abnormalities such as optic atrophy and macular degeneration are seen in all NCL types except Kufs disease.

In cases of new onset of refractory EPC, an autoimmune etiology should be suspected, particularly if associated with symptoms suggestive of a limbic encephalitis such as a history of viral prodrome, associated psychiatric symptoms, prior history of tumor, or absence of structural abnormality on imaging. These patients should have serologic tests for infectious, autoimmune, and paraneoplastic causes. Cerebrospinal fluid should be tested for infectious (viruses, parasites, fungi, and syphilis, and borrelia), paraneoplastic, and autoimmune etiologies. Evidence of CSF inflammation may be present, including serologic markers of systemic autoimmunity (ANA or TPO); elevated protein, pleocytosis, oligoclonal bands, elevated IgG index on CSF; areas of hypermetabolism on brain PET, or areas of hyperintensity on

FLAIR/T2 brain MRI imaging. The EEG in NMDA encephalitis patients may show a typical "extreme delta brush" pattern [78].

Prognosis

Prognosis of MSE depends on the type of MSE and the underlying disorder. Primary MSE is usually treatable and responds to treatment with intravenous benzodiazepines, valproate, or levetiracetam. Removing a potential ASD that aggravates MSE is important. In JME, the risk of MSE diminishes with age, as myoclonus tends to disappear or diminish in severity after age 30 years [79].

The prognosis of secondary forms of MSE depends on the type of epilepsy and the length and frequency of the myoclonic status. For symptomatic generalized epilepsies, MSE tends to be refractory and often relapses after temporary control has been achieved. In myoclonic-astatic epilepsy, early presentation and longer duration of MSE has been associated with an increased risk of dementia. The prognosis in EPC is often poor. Patients may develop cognitive deficits and chronic neurologic deficits with weakness, sensory and visual loss, and language dysfunction [51]. In a study following 32 patients with EPC, 15 died over a follow up period of 3 years. The causes of death were either the disease causing EPC or the immediate complications of the disease [49].

Prognosis in symptomatic MSE is good when due to a reversible cause, such as uremia or drug intoxication, and usually resolves with removal of the underlying toxin. In patients affected by PME, MSE is seen prominently in the late phase of the disease, but that stage is often refractory to medications.

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Anoxic Myoclonic Status Epilepticus

13

Gerhard Bauer and Iris Unterberger

Use of Terms

The term *hypoxic-ischemic encephalopathy* is used for brain injury after cardiac compromise including cardiac arrest (CA), profound hypotension, pure respiratory arrest, and intoxications, sharing a final common pathway of neuronal death from failure of oxidative metabolism [1]. These conditions following CA are also termed *post cardiac arrest syndrome*. Ischemia and hypoxia usually coexist. Different phases and pathophysiologic components have been described [2].

Myoclonus is involuntary, quick, visible jerks—to be distinguished from peripheral or complex hyperkinetic abnormalities [3]. Myoclonus includes either abrupt muscle contraction (positive myoclonus) or sudden cessation of ongoing muscle activity (negative myoclonus) [4]. Myoclonus may originate from the cerebral cortex, from subcortical cerebral structures, or from the spinal cord, with some clinical, etiologic, and anatomic characteristics [3, 4]. Concomitant epileptiform electroencephalography (EEG) discharges signify *cortical epileptic myoclonus. Subcortical myoclonus* is considered a release phenomenon, and no spikes are recorded at the scalp surface [5]. Ongoing myoclonic activity of cortical or subcortical origin, or both, is termed *myoclonic status. Myoclonic status epilepticus* is classified as a condition with prominent epileptic myoclonic jerks, with or without coma [6].

Incidence of Seizures and Neurological Signs in Hypoxic-Ischemic Encephalopathy

After CA, most surviving patients are treated in intensive care units (ICU), where neurologic signs and seizures may be masked by the use of paralytic agents, sedatives, and muscle relaxants. After cardiopulmonary resuscitation the incidence of seizures including myoclonus ranged from 12 to 44% [7]. Among comatose survivors, 45% had continuous myoclonus for more than 30 min, corresponding to anoxic myoclonic status epilepticus (AMSE) [8]. Brainstem reflexes are absent, and extensor motor responses (or none) are seen [9]. The limb jerking of postanoxic myoclonus differs from that of the midbrain and bulbar stages of coma with herniation, in that it also often involves the face and may be subtle, with low-amplitude jerks, but without posturing, and often, it can be triggered by loud sounds or clapping. Sometimes, it may be difficult to distinguish from the jerking seen with herniation.

Semiology of Motor Anomalies in Hypoxic-Ischemic Encephalopathy

Myoclonus after hypoxic insults is highly variable, ranging from single jerks to AMSE [10]. In two thirds of patients, myoclonus is generalized; in one third multifocal [11]. Single jerks in postanoxic coma are frequently triggered by exogenous stimuli, occasionally area specific [12, 13]. *Anoxic myoclonic status epilepticus* (AMSE) occurs in coma and is characterized by spontaneous, periodically repeated, axial and bilaterally synchronous jerks of limb, trunk, or facial muscles [14]. AMSE starts at any time after the return of cerebral circulation [9, 14]. Exogenous stimuli may alter the endogenous repetition rate [11].

Besides myoclonus, a number of other abnormal motor phenomena can be observed after CA. An incompletely analyzed phenomenon is *myoclonic shivering*. Snyder and colleagues defined it as frequent rhythmic, rapid, low-amplitude limb and facial movements, mostly evident in the immediate aftermath of resuscitation [15]. The mechanism and prognostic significance remain unclear, as does its distinction from continuous, irregular facial twitching (Figs. 13.1 and 13.2) or early postanoxic myoclonic jerks

G. Bauer (✉) · I. Unterberger
Department of Neurology, Medical University of Innsbruck, Anichstrasse 35, 6020 Innsbruck, Tyrol, Austria
e-mail: Gerhard.Bauer@i-med.ac.at

I. Unterberger
e-mail: iris.unterberger@tirol-kliniken.at

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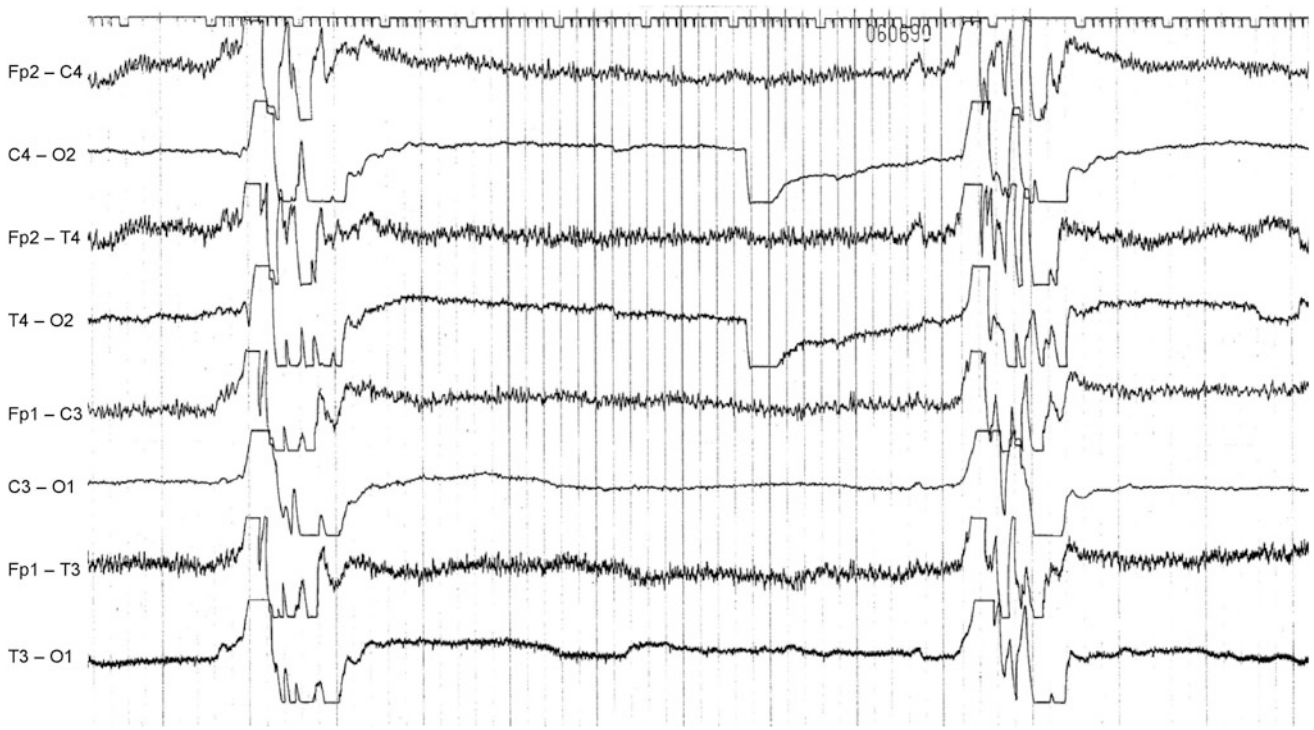

Fig. 13.1 Electroencephalogram (EEG) of a 70-year-old woman. Cardiac arrest with cardiac infarction. Comatose, on respirator, no visible myoclonic jerks. Generalized periodic discharges-burst suppression pattern. No identifiable cortical activity amidst abundant muscle artifact due to irregular facial twitches (EEG: time constant [TC] 1.0, high-frequency filter [HFF] 70; double distance electrode placement)

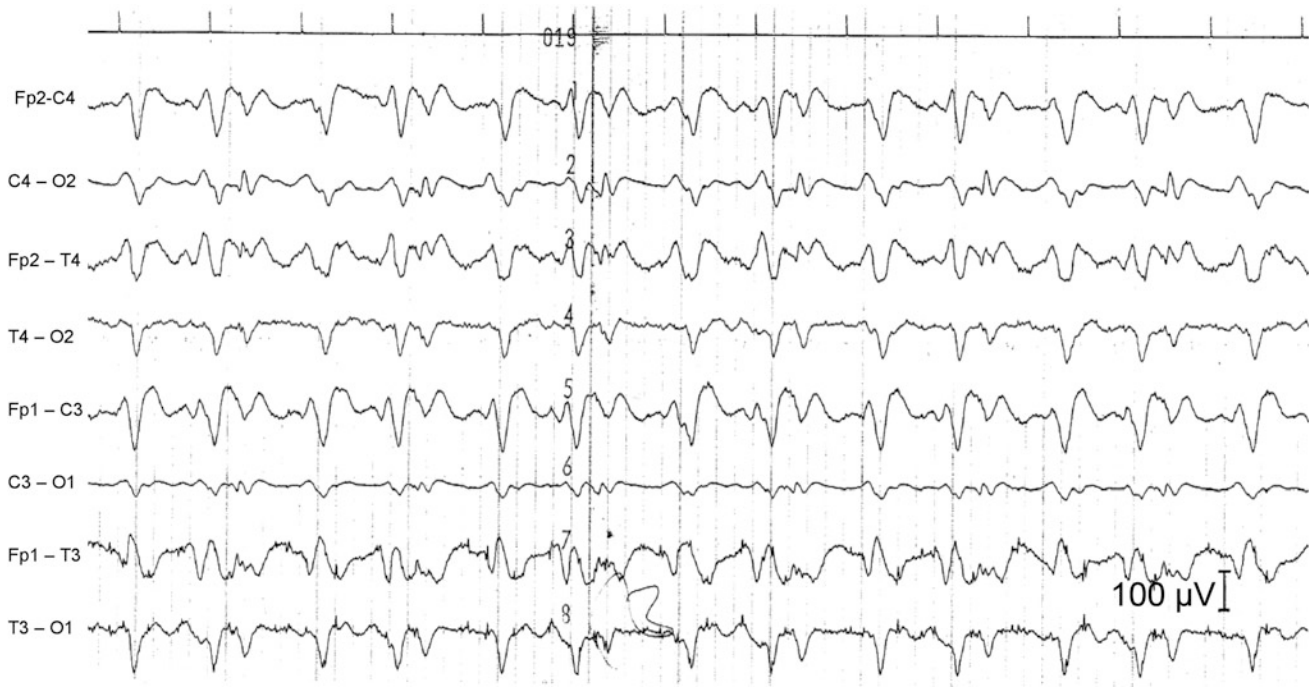

Fig. 13.2 Electroencephalogram (EEG) of a 67-year-old man. Coma after cardiac arrest. Facial twitching (see muscle artifact). 1/s rhythmic bilateral triphasic waves (EEG: time constant [TC] 0.3, high-frequency filter [HFF] 30)

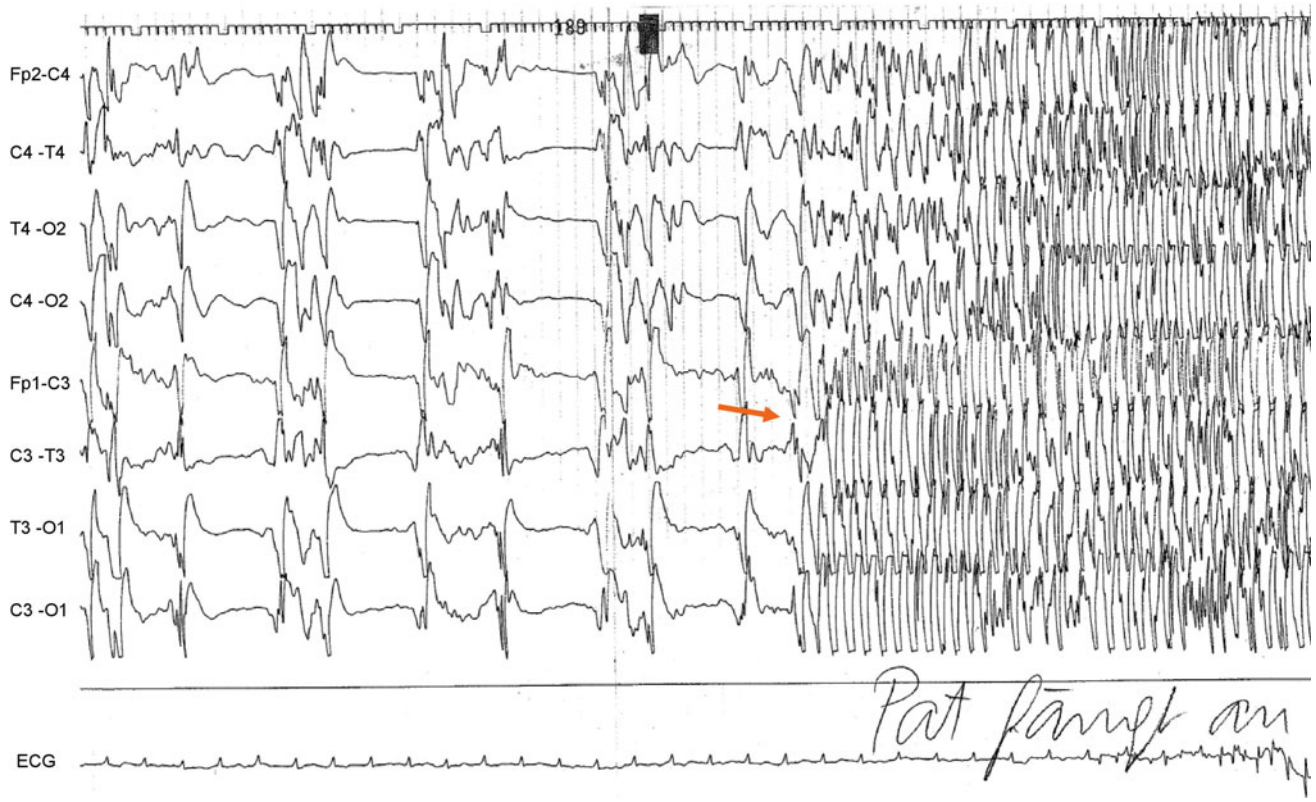

Fig. 13.3 Electroencephalogram (EEG) of a 65-year-old woman. Comatose after vascular infarct and cardiac arrest. No visible jerks. Generalized eperiodic discharges-burst suppression pattern, with short intervals. Development of a generalized seizure pattern ("*Pat fängt an*" = *pattern begins*) with a right central start (*arrow*). Clinically classified as "trembling" seizure (EEG: time constant [TC] 0.3, high-frequency filter [HFF] 70)

[16, 17]. Myoclonic shivering exhibits some phenomenological similarities with shivering in hypothermia, with trembling epileptic seizures (Fig. 13.3), and with convulsions during cardiac syncope [18]. *Generalized tonic–clonic seizures* occur along with AMSE in one third of patients [15, 19]. *Focal motor seizures* are also observed [18, 20–22].

Tonic eye opening in postanoxic coma may confuse physicians and families, as it incorrectly suggests possible awakening [11, 18, 22–24] (Fig. 13.4). This often occurs spontaneously at a periodic repetition rate that can be affected by painful stimulation. Time-locked generalized epileptiform EEG discharges and the co-occurrence of generalized jerks support the interpretation that this is cortical epileptic myoclonus. Myoclonus can also be restricted to jaw opening [11] or to the abdominal muscles [25].

Myoclonus must be differentiated from subcortically mediated abnormal postural rigidity exaggerated to jerk-like movements by stimulation [26]. In contrast to cortical myoclonus, posturing exhibits no concomitant epileptiform EEG changes except for artifacts (Fig. 13.5). Posturing has been considered subcortical myoclonus, i.e., a release phenomenon produced by subcortical structures [5]. Continuously occurring muscle artifact on the EEG can be related to severe rigidity (see Fig. 13.1) and should not be confused with myoclonic shivering.

Myoclonus in the Lance–Adams syndrome follows hypoxic brain injury due to an acute asthmatic attack, or brief CA, but without marked irreversible cortical infarction [27, 28]. Multifocal cortical action myoclonus in Lance–Adams syndrome typically emerges after the patient regains consciousness. It may be alleviated by anti-seizure drugs (ASDs) and has a tendency to resolve with time. Nonetheless, it may persist for weeks to months, if not years.

EEG Abnormalities in AMSE

EEG recording can be carried out in the ICU without harm to the patient, has low costs, and can be performed repeatedly, or monitored continuously. Continuous EEG monitoring offers no significant advantages over intermittently repeated standard recordings [29].

AMSE is characterized by a stereotyped sequence of generalized discharges (*generalized periodic discharges,* GPDs) on a profoundly abnormal background (Figs. 13.1, 13.2, 13.3, 13.4c, 13.6a, 13.7, 13.8). Generalized bursts

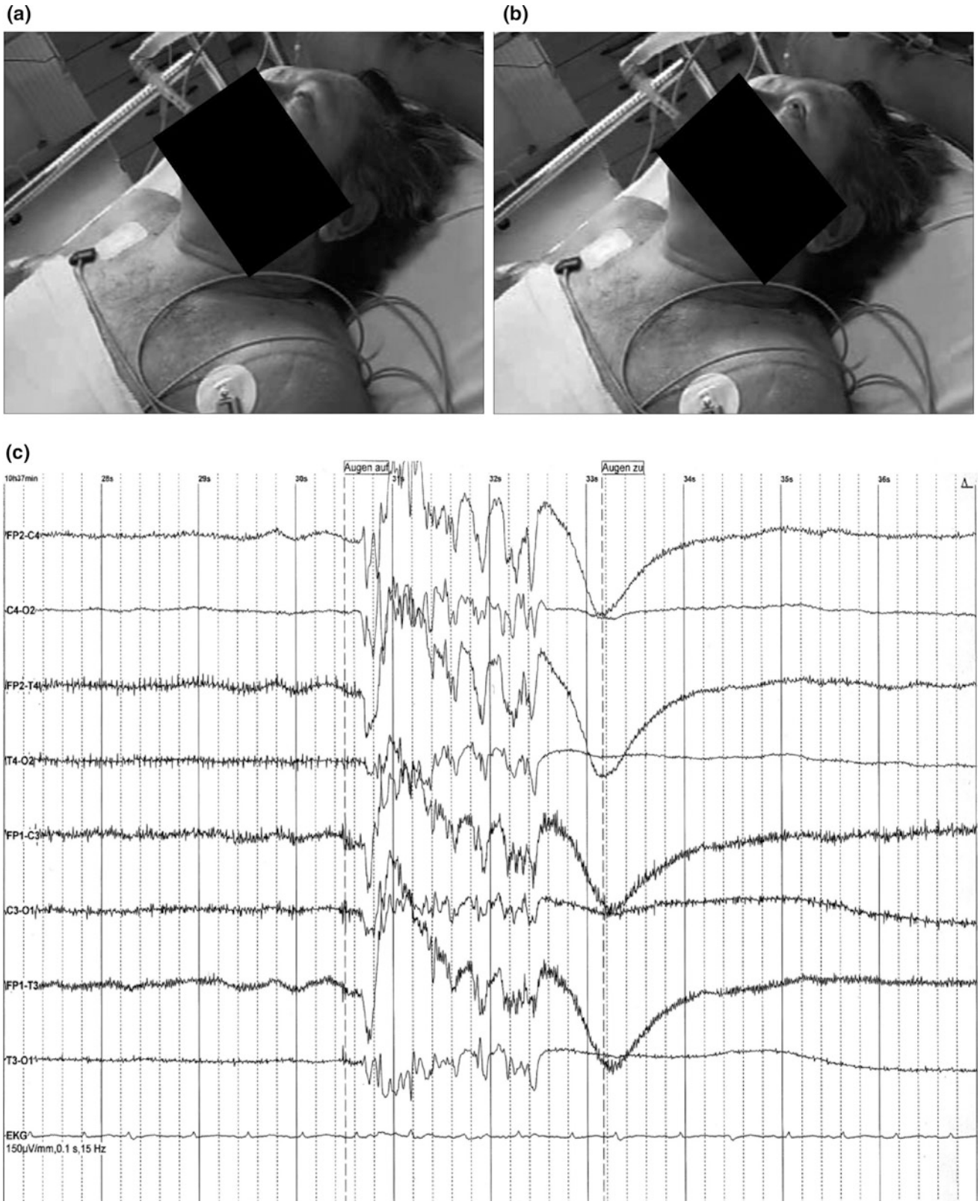

Fig. 13.4 Electroencephalogram (EEG) of a 70-year-old man. Coma after cardiac arrest. Frames of a video tape: **a** Eyes closed. **b** Eyes periodically opened. Time locked to eye opening are bilateral myoclonic jerks and generalized periodic discharges on the EEG (**c**). Flat record in the interval, with superimposed muscle artifact (From Unterberger et al. [18], with permission)

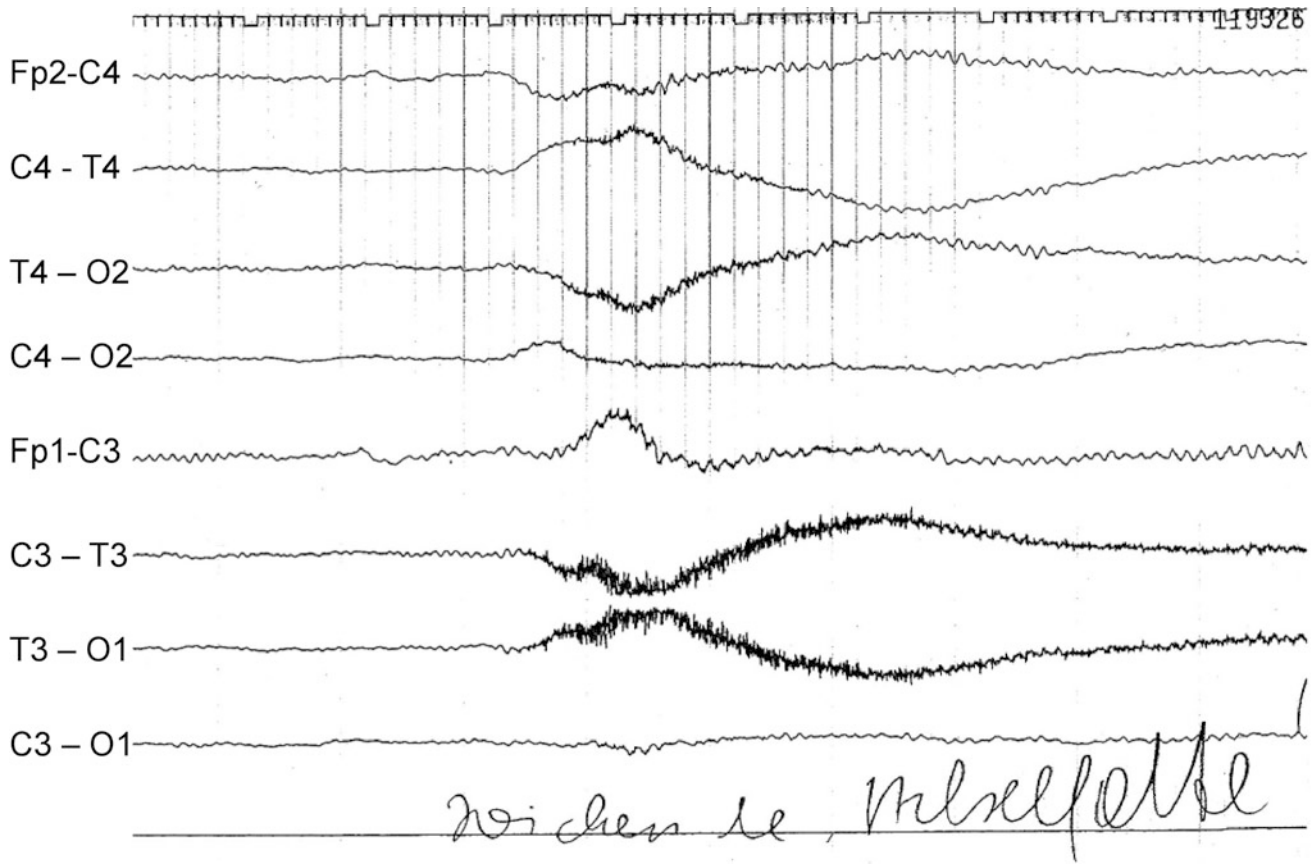

Fig. 13.5 Electroencephalogram (EEG) of a 66-year-old man. Anoxic myoclonic status epilepticus after cardiac arrest. After cessation of jerks, alpha coma on the EEG. Decorticate posturing, exaggerated with stimulation ("*zwicken re Achselfalte*" = pinch in axillary fold). Artifacts and increase of amplitude, without epileptiform discharges (EEG: time constant [TC] 0.3, high-frequency filter [HFF] 70)

include spikes, spikes and waves, sharp waves, slow activity or combinations of these. Critical care EEG terminology has been standardized by Hirsch et al. [30], and *post hoc* surveys showed substantial inter-rater agreement in the use of these terms [31–33]. GPDs are time-locked to jerks, but in many cases, GPDs occur without visible motor signs. Jerks may be suppressed in the ICU by treatment with paralytic agents, sedatives, and anesthetic agents. Without superficial electromyogram recording, inconspicuous fine jerks may be missed. These coma cases have frequently been termed nonconvulsive status epilepticus (NCSE), but GPDs are also seen in advanced nonepileptic coma states, including those due to sedative-antiseizure drugs [1] or with hypothermia for surgical intervention [34]. Therefore, Bauer and Trinka [35] distinguished coma with GPDs after hypoxia from NCSE "proper" in the categorization of the epilepsies.

Such typical EEG patterns may be confined to selected segments of the EEG monitoring, and fluctuations and transitions are the rule in a given record or with repeated recordings [11, 36]. *Generalized and focal seizure patterns* may interrupt the periodicity (for a 2006 review, see Kaplan [37]) (see Fig. 13.3). Frequently, seizure patterns are clinically nonconvulsive or subtle and therefore termed electrographic or subclinical [38, 39]. Periodic lateralized epileptiform discharges (PLEDs) or *lateralized periodic discharges* (LPDs) after Hirsch and colleagues [30] can fluctuate with GPDs and suggest a localized lesion such as an infarction (see Fig. 13.6).

Suppression-burst activity represents a distinct type of GPDs. Periodic high voltage generalized bursts alternate with nearly isoelectric activity in a quasi-periodic fashion [40]. Suppression-burst activity is often an EEG correlate of AMSE; of coma without motor seizures; of periodic tonic eye opening (see above); or of oral, ocular, or appendicular subtle movements [24]. Modifiers include the length of intervals, the type of background activity, and burst morphology (see Figs. 13.1, 13.3, and 13.6a). Like other forms of GPDs, suppression-burst activity probably shares a common mechanism across diverse etiologies that cause oxygen and glucose deprivation [41].

Triphasic waves or continuous 2/s GPDs with triphasic morphology [30] were first described in hepatic coma but afterwards in a variety of encephalopathies, including post cardiac arrest syndrome (for summary, see Kaplan and Bauer, [1]). Typical and atypical forms have been described,

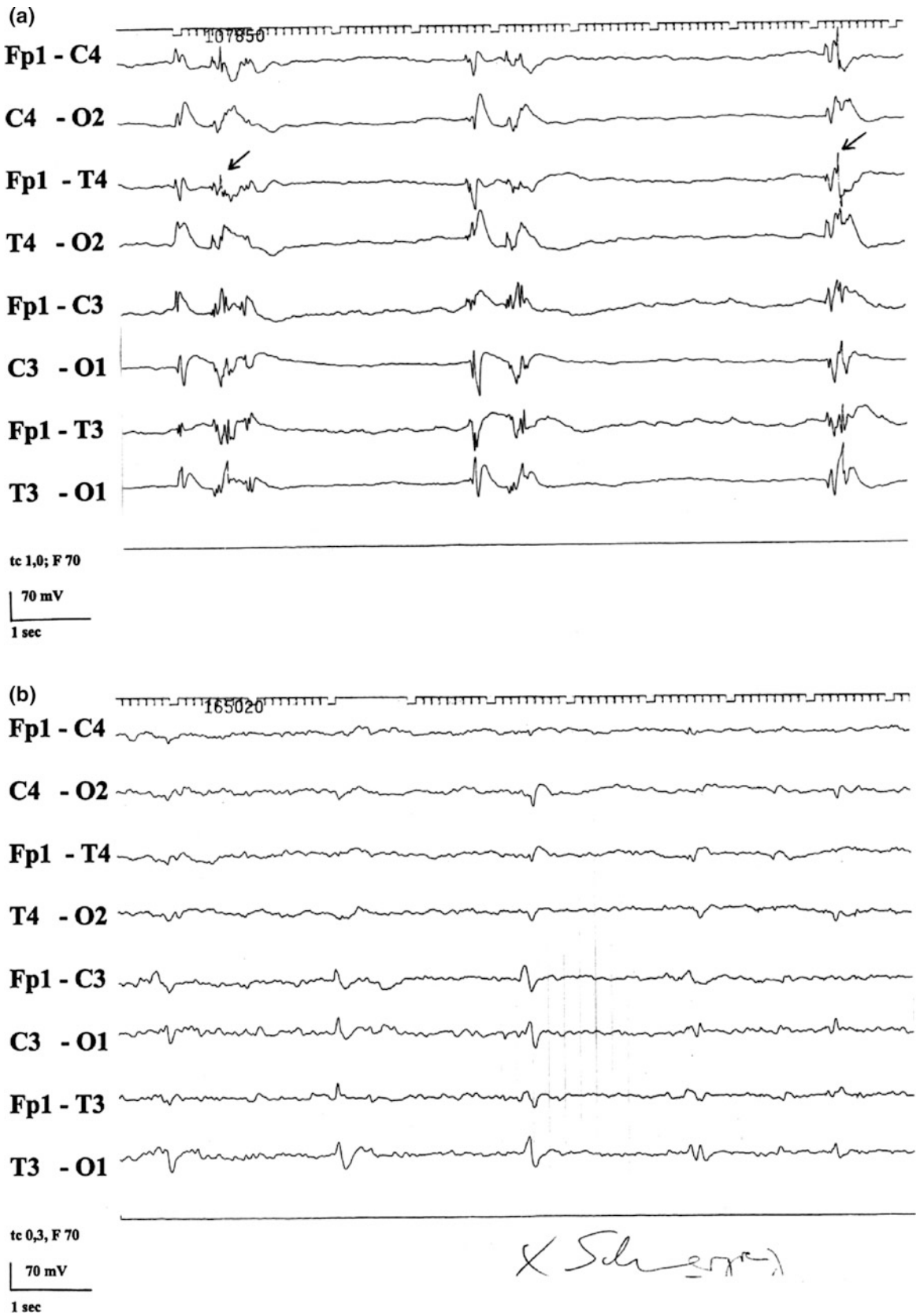

Fig. 13.6 Electroencephalogram (EEG) of a 49-year-old man. Head trauma, acute symptomatic seizure, hypoxic episode. Comatose, on respirator, anoxic myoclonic status epilepticus time locked to generalized periodic discharges, accentuated over left hemisphere. **a** Muscle artifact due to jerks (*arrows*). In **b** lateralized periodic discharges (LPDs); no change with painful stimuli ("*Schmerz*" = pain). Alpha–theta frequencies between LPDs (from Bauer et al. [36], with permission)

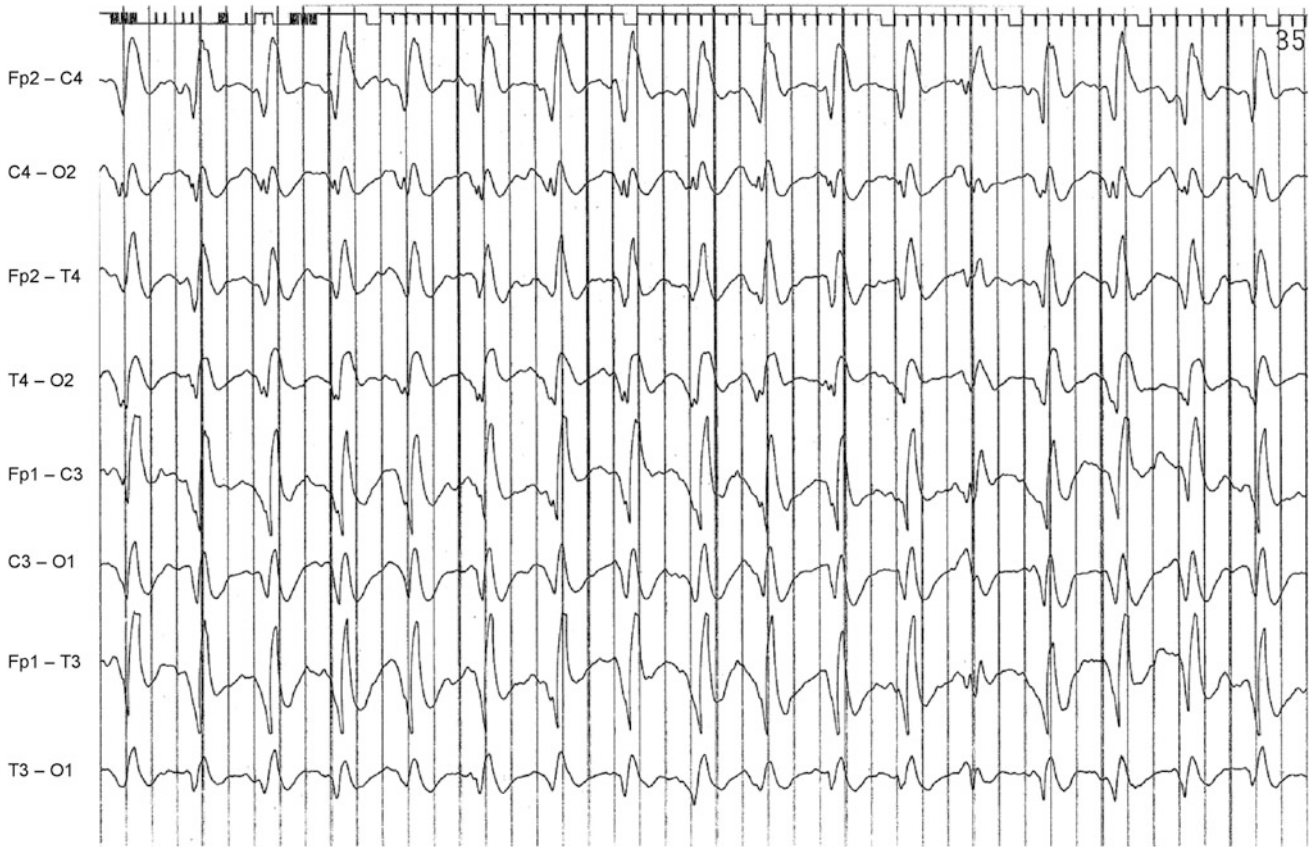

Fig. 13.7 Electroencephalogram (EEG) of a 60-year-old woman. Coma after cardiac arrest. Irregular diffuse myoclonic twitches. Generalized 2/s triphasic waves. Note the preceding small spikes, best recognized in channel 2. No change after i.v. phenytoin (EEG: time constant [TC] 0.3, high-frequency filter [HFF] 70)

but the diagnostic significance of any type remains to be established [42]. Triphasic-appearing waves have been recorded in myoclonic status epilepticus, in degenerative and spongiform encephalopathies, and in atypical absence status in the Lennox–Gastaut syndrome [1]. The clinical condition associated with triphasic waves after hypoxia is often considered NCSE; abnormal motor activity (see Figs. 13.2 and 13.7) has not been analyzed specifically.

Stimulus-induced rhythmic, periodic, or ictal discharges (SIRPIDs) were originally reported in critically ill patients [43]. Alvarez and colleagues analyzed the role of SIRPIDs in post cardiac arrest syndrome [44]; 14 of 105 patients had SIRPIDs, 5 of them with early myoclonus. The pattern lies somewhere along an ictal-interictal continuum [45].

The importance *of EEG reactivity to exogenous stimulation* has been stressed repeatedly [17, 46–48]. Hirsch and colleagues refined types of reactivity using their critical care EEG terminology [30], and a systematic description was proposed. Rossetti and colleagues assessed the reactivity (regardless of the appearance of epileptiform transients), and differentiated nonreactive records from reproducible changes in *background EEG* [17]. In a retrospective study of hypoxic-ischemic injuries, Howard and colleagues differentiated responsive from non- or poorly responsive EEG rhythms, and from low-voltage background activities [46]. Bauer and colleagues collected several types of EEG reactivity in the post cardiac arrest syndrome in a retrospective observational study [36]. Some studies showed that arousal can lead to a breakdown of electrical activity that may be difficult to distinguish from spontaneous EEG voltage attenuations. In summary, reactions to exogenous stimuli are manifold; their classification and correlation to clinical variables have not been studied systematically.

In AMSE, GPDs may alternate with rhythmic *alpha-or theta frequencies* (see Figs. 13.6b and 13.8). Furthermore, transitions from GPDs to continuous alpha/theta rhythms have been observed [49] (see Fig. 13.5). A long-standing debate involves the prognostic significance and differential diagnosis of different alpha frequencies in coma or in the locked-in syndrome [49]. Reactivity of alpha frequency activity predicted good outcome in an etiologically mixed sample [50]. Berkhoff and colleagues reinvestigated post-anoxic alpha (theta) coma and distinguished complete and incomplete forms [51]. Complete forms correspond to the

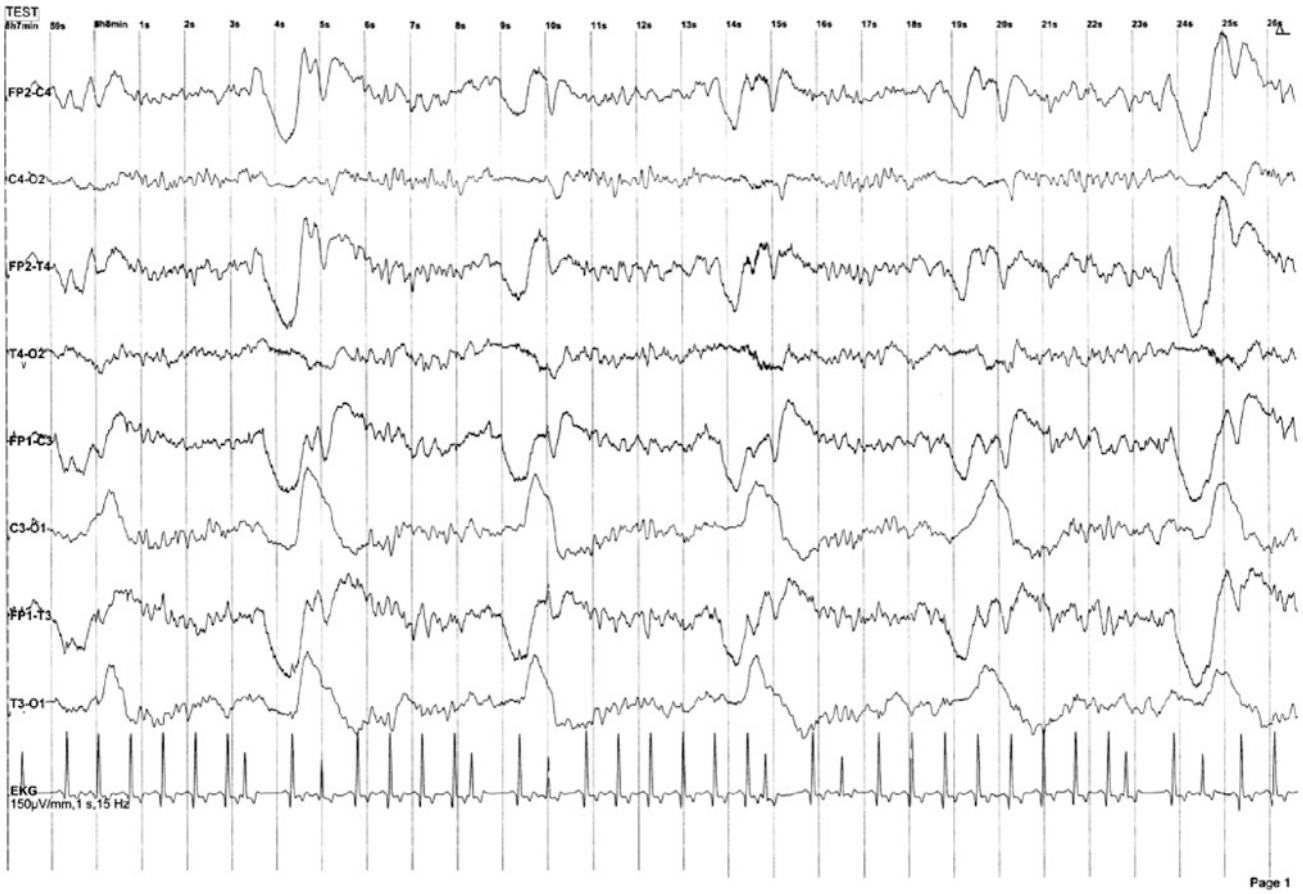

Fig. 13.8 Electroencephalogram (EEG) of a 41-year-old man. Hypoxic coma, no visible motor abnormalities. Periodic slow waves (generalized periodic discharges), with nonreactive alpha-theta rhythms in between. (EEG: time constant [TC] 0.3, high-frequency filter [HFF] 15, 7 µV/mm, reduced paper speed)

original description of alpha coma and signify a poor prognosis [52].

Evoked Potentials, Biomarkers, and Neuroimaging Methods

In the post CA syndrome, the bilateral absence of the N20 component of the somatosensory evoked potentials with median nerve stimulation, recorded on days 1–3 or later after CA, accurately predicts poor outcome, as do serum neuron-specific enolase levels of >33 µg/L at days 1–3 [9]. Neuroimaging methods in this setting have been summarized by Little and colleagues [53] and have their pros and cons [54]. Despite some reports claiming prognostic superiority over conventional tools [55, 56], the value and reliability of imaging methods remain inconclusive. Furthermore, imaging typically involves moving the patient, which can be difficult or may be harmful to a patient in the ICU.

All methods mentioned above have been used in the study of the post CA syndrome in general. No specific data can be found regarding clinically and electroencephalographically proven AMSE.

Therapeutic Measures and Prognosis

Treatment and prognostic statements in this section refer to postanoxic states in general. Coma with periodic epileptiform EEG abnormalities has been considered a type of NCSE, and these same EEG discharges are the hallmark of AMSE. The differential diagnosis between NCSE and AMSE depends on the observation of motor abnormalities—frequently abolished by neuromuscular blocking agents used in the ICU management of patients. Furthermore, in dosages used for treatment of these patients, sedatives and ASDs may produce periodic EEG changes themselves. Thus, diagnostic and prognostic statements regarding postanoxic coma depend on conceptual and observational uncertainties, and can be affected by the effects of sedating medication.

A long list of papers stresses the dismal prognosis of coma with AMSE and GPDs [16, 57–60]. Besides ICU treatment,

ASDs and *hypothermia* have been tried. The Hypothermia after Cardiac Arrest Study Group confirmed the therapeutic effect of hypothermia in post cardiac arrest syndrome in general [61]. In AMSE, the beneficial role is less well established. AMSE can occur before and during hypothermia and with rewarming. Wijdicks and colleagues stated that patients with myoclonic status epilepticus within the first day after a primary circulatory arrest have a poor prognosis [9]. This is also true for hypothermia-treated patients with status epilepticus [62].

Several papers, however, have reported good outcome in early posthypoxic myoclonus in which the etiology for these coma states was respiratory arrest [63–66]. After the subject's regaining consciousness, the diagnosis of Lance–Adams syndrome was established. A good neurologic outcome was reported in three cases of primary cardiac arrest syndrome and myoclonic status treated with hypothermia [67]. It was concluded that premature, pessimistic prognostic statements should be reconsidered.

Hofmeijer and van Putten reviewed the prognostic and diagnostic value of EEG in postanoxic coma [68]. Drug-induced burst-suppression patterns are claimed to be different from those due to the hypoxic insult itself. The EEG pattern of "burst suppression with identical bursts" was characteristic of hypoxia with a poor outcome. Evolution of EEG changes over repeated records and reactivity of background activity have additional predictive value. The therapeutic effect of ASD treatment has not been demonstrated, but epileptiform EEG abnormalities in AMSE are rarely changed by i.v. ASDs (see Fig. 13.7). Several cases with reactive EEGs, intact brainstem function, and some discernible background rhythms may have a favorable outcome when treated with hypothermia [47]. Aggressive ASD treatment of SE arising during hypothermia seems futile [69]. EEG patterns with unfavorable prognostic significance remain so even with hypothermia [70].

The diagnostic verification and documentation of AMSE is of crucial importance. Nonepileptic motor abnormalities seen in postanoxic coma must be differentiated from epileptic myoclonic jerks. In cases of unequivocal AMSE, a meaningful recovery seems to be a very rare development. Death, permanent vegetative state (unresponsive wakefulness syndrome [71]), or a minimally conscious state [72] form the tragic outcome triad in cases of AMSE.

Conclusions

Except for brain death syndrome and for coma with a very low-voltage EEG, AMSE represents the most advanced stage of postanoxic coma. Periodically repeated bilateral cortical myoclonus is a hallmark of this fatal condition. GPDs in the EEG are time locked to myoclonus and corroborate the epileptic nature of this seizure type. Motor abnormalities with periodic EEG abnormalities other than AMSE should be evaluated carefully. In questionable cases, median nerve somatosensory evoked potentials and imaging methods may improve diagnostic and prognostic accuracy. In order to avoid a self-fulfilling prophecy, a prolongation of the time of observation is recommended in doubtful cases. ASDs and treatment with hypothermia may be tried but should be stopped in cases that do not remit, or after the reappearance of myoclonic jerks, GPDs or both. This tragic situation requires psychologic and psychiatric support for relatives and other loved ones.

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Tonic, Clonic, and Atonic Status Epilepticus

14

Mary Kurian and Christian M. Korff

Introduction

The International League Against Epilepsy has recently revised the definition and classification of status epilepticus (SE), as mentioned in Chap. 2, "Types of SE: Definitions and Classification." In this proposal, various types of SE are categorized according to Semiology, Etiology, Electroencephalography (EEG) findings, and Age [1]. The main semiologic categories of SE can be identified according to the presence or absence of prominent motor symptoms and the degree of impairment of consciousness [1]. Further subdivisions are made according to specific types of ictal motor activity and generalized or focal onset of symptoms. Convulsive SE is characterized by repetitive motor manifestations and occurs with overt clinical signs such as tonic-clonic, myoclonic or clonic movements, and tonic postures. The basic EEG characteristics for the different electroclinical types of SE include rhythmic activity, epileptiform discharges, and often a waxing and waning evolution [2]; SE is a dynamic disorder. If seizure activity is allowed to persist without successful treatment, the behavioral and electrical manifestations evolve over time. The purpose of this chapter is to present the current state of knowledge about various aspects of three specific forms of SE not covered elsewhere in this book: tonic, clonic, and atonic SE.

M. Kurian · C.M. Korff (✉)
Pediatric Neurology Unit, University Hospitals of Geneva, 6 Rue Willy-Donzé, 1211 Geneva 14, Switzerland
e-mail: christian.korff@hcuge.ch

M. Kurian
e-mail: marykurian@me.com

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Tonic Status Epilepticus

Clinical Presentation and Context

Tonic status epilepticus (TSE) manifests with repetitive series of frequent tonic seizures that may last for days or weeks. As the status progresses, autonomic manifestations, including respiratory depression, may predominate and lead to death. Exceptionally long TSE, persisting for 5 months, has been reported [3].

The specific pathophysiology of TSE is unknown. Tonic seizures have been thought to be due to involvement of brainstem structures [4], thalamus, and frontal cortex [5–7]. TSE almost always consists of a series of relatively brief tonic seizures repeated at varying intervals, leading to the maintenance of a prolonged posture. The contractions may involve the face, axial and proximal limb musculature, and the extremities in various combinations [2]. A vibratory phase, consisting of low amplitude and very rapid contractions, may be observed and wrongly interpreted as clonic phenomena. Clinical symptoms may be mild, showing only low-amplitude tonic contractions of paraspinal musculature or upward deviation of the eyes [8]. Tonic seizures usually last less than 10 s but can recur many times in a day. Given the subtle presentation that may occur and the large differential diagnosis to consider (which includes acute dystonic postures due to metabolic conditions, reactions to certain drugs, gastro-esophageal reflux, or other types of seizures such as epileptic spasms), an electroencephalogram (EEG) is necessary to make the diagnosis of TSE. The EEG may show widespread symmetric fast activity, very rapid spikes, background suppression or attenuation, generalized electrodecremental activity, or brief runs of low-voltage generalized fast activity [8]. TSE may be difficult to stop with antiseizure drugs, and certain medications, such as diazepam, lorazepam [9, 10], or valproate [11, 12] may precipitate or worsen TSE in some cases.

For the most part, TSE occurs in young patients with major neurologic and cognitive deficits or other

encephalopathies from birth or childhood, e.g., conditions such as Ohtahara syndrome in the neonatal period and Lennox–Gastaut syndrome (LGS) in older children [1].

TSE is rare in adults in the absence of other seizure types [8]. A single patient presenting with generalized TSE and Creutzfeldt-Jakob disease and hyperparathyroidism has been reported [13]. Other patients manifest confusion or unresponsiveness [14, 15] as the sole apparent symptom of TSE, which highlights the diagnostic challenge that this condition poses; such cases remain exceptional. Infrequently, TSE may occur in patients with genetic generalized epilepsies (GGE) [12, 16], as discussed later.

Tonic Status Epilepticus in Ohtahara Syndrome

Clinical manifestations of neonatal seizures are often different from those in other age categories, due to incomplete synaptic connectivity and immature cortical structures. Ictal motor activity may be more polymorphic and poorly organized, some seizures resembling only isolated fragments of seizures in older individuals. Tonic seizures are nevertheless a common neonatal seizure type, especially in the premature [17]. Typically, the child will present with a rapid extension of all limbs accompanied by apnea and sometimes, upward eye deviation, and tremor of the extended limbs; some seizures are stimulus-sensitive. Characteristic features of Ohtahara syndrome, or early infantile epileptic encephalopathy (EIEE), include tonic spasms with an interictal burst suppression EEG pattern that consistently occurs in both sleeping and waking states [18]. The tonic spasms consist of forward tonic flexion lasting 1–10 s, which may occur in long clusters of repeated seizures, thereby producing TSE [18].

Tonic Status Epilepticus in Lennox–Gastaut Syndrome

Lennox–Gastaut syndrome (LGS) is characterized by intractable, multiple generalized seizure types and an interictal EEG showing bursts of slow spike-and-waves, paroxysmal bursts of generalized or multifocal polyspikes, and a slow background. It is frequently associated with underlying central nervous system defects. Nocturnal tonic seizures are a hallmark of LGS [19].

Tonic seizures in LGS manifest by brief or more sustained contractions of the arms, often accompanied by uprolling of the eyeballs, contraction of the face, neck, and throat muscles, and extension of the legs. The repetition of tonic contractions may appear every few minutes without return to baseline, consistent with TSE. The violent and sustained flexion of the spine may produce vertebral collapse [2]. Pure tonic SE in LGS is observed more often in adolescents than in children [4]. It is usually characterized by tonic seizures occurring subcontinuously during waking and sleep, and may be intermixed with generalized tonic-clonic seizures. Swallowing difficulties and autonomic dysfunction, with respiratory failure, tachycardia, and hyperthermia may occur [4]. The ictal EEG may show desynchronization, but more typically includes low-voltage fast activity at 20–30 Hz that gradually slows down to 10–20 Hz while increasing in voltage [2]. Intermixed discharges of slow spike-waves may be present. Stuporous states are associated with mixed irregular diffuse or anterior slow spikes or polyspike-waves [4].

LGS has a poor prognosis. Only rarely do patients achieve seizure control, and profound intellectual disability and behavioral abnormalities are the rule. It remains uncertain whether TSE per se carries a prognostic importance in LGS.

Tonic Status Epilepticus in Genetic Generalized Epilepsies

TSE in patients with the GGE is uncommon. Kobayashi and colleagues reported episodes of tonic seizures in clusters in three patients with GGE, but duration of the clusters and cognitive state between seizures was not described [16]. The question whether repeated tonic seizures in these patients had therapeutic (response to antiseizure drugs) or prognostic implications remained open. More recently, a child with Doose syndrome and valproate-induced TSE was reported [12].

Therapy and Prognosis

TSE may be resistant to standard anticonvulsants and is potentially lethal. No specific therapeutic approach for TSE has emerged recently. In addition to "standard" therapeutic recommendations, the use of lacosamide may be considered, including for teenagers [20, 21]; two reported patients responded to a single intravenous dose of 100 mg, while one required two doses for seizure termination.

Clonic Status Epilepticus

Clinical Presentation and Context

Clonic SE is defined as "prolonged episodes of repetitive, brief muscle contractions occurring in a rhythmic fashion

and involving the same muscles or migrating to somatotopically contiguous muscle groups ('Jacksonian march')" [22]. Clonic SE is relatively rare in adults and occurs predominantly in infants and children, often in association with fever [8]. It may also be seen in patients with developmental delay, usually in the setting of LGS. The clinical correlate is that of repeated, rhythmic, clonic jerks that may be generalized, bilateral, asymmetric, or arrhythmic. The EEG is variable, typically showing bilateral bursts of high amplitude delta slowing with spikes or polyspikes, often occurring synchronously with clonic jerking. It may show bursts of spikes or recruiting rhythms that then progress to spike-waves [2]. Various clinical situations in which clonic SE may be observed are presented.

Clonic Status Epilepticus in Dravet Syndrome

Dravet syndrome is a severe infantile-onset epilepsy syndrome with a distinctive electroclinical presentation. Convulsive SE, often clonic and unilateral, typically occurs in a healthy, developmentally normal infant at around 6 months of age. Seizures are frequently triggered by fever due to illness or vaccinations. The infant typically has further episodes of SE, and various additional seizure types appear such as myoclonia, generalized tonic-clonic seizures, atypical absences, and episodes of nonconvulsive SE. Early development is normal but slows in the second year. EEG studies are normal initially, but usually show generalized spike-wave and polyspike-wave activity with multifocal discharges on evolution [23]. Imaging is normal or shows nonspecific findings such as global atrophy. Intellectual disability and ongoing seizures are present in most patients.

Clonic Status Epilepticus in Hemiconvulsion–Hemiplegia Epilepsy

Hemiconvulsion–Hemiplegia Epilepsy Syndrome (HHS) is a rare and severe epilepsy of infancy consisting of unilateral convulsive SE followed immediately by transient or lasting ipsilateral hemiplegia with pharmacoresistant epilepsy [24]. SE can occur in a previously healthy child during or closely after a febrile episode [25]. HHS may occur without any identified cause—so-called "idiopathic HHS" (IHHS). IHHS begins in infancy with unilateral clonic SE, usually occurring during the course of a febrile illness, and is followed by hemiplegia ipsilateral to the side of convulsions. This is accompanied by radiologic evidence of acute cytotoxic edema in the affected hemisphere, followed by chronic cerebral atrophy [26]. The pathophysiology of HHS remains poorly understood, the long-term outcome is poor, and a fatal outcome has also been reported [27].

Clonic Status Epilepticus in Metabolic Diseases

Clonic SE may represent a manifestation of various metabolic diseases, without specificity. For instance, in children with Menkes disease, a rare X-linked recessive neurodegenerative disorder resulting from a mutation in the gene coding for the copper transporting ATPase (ATP7A), epilepsy has been described as involving three steps: an early stage with focal clonic seizures and SE, an intermediate stage with infantile spasms, and a late stage with multifocal, myoclonic, and tonic seizures [28]. Menkes disease has been recently reported to present with *epilepsia partialis continua* (EPC) in a seventeen-month-old infant [29].

Focal Tonic Status Epilepticus and Underlying Cortical Lesions—Epilepsia Partialis Continua

Focal motor SE is readily recognized and thus, clonic SE may actually start as a focal clonic seizure due to any underlying lesion, such as acute stroke [33], tumor [34], cortical dysplasia, or tubers. *Epilepsia partialis continua* (EPC) is a continuous seizure type presenting as irregular clonic twitching of cortical origin, sometimes aggravated by action or sensory stimuli, confined to one part of the body and continuing for extended periods [30, 31]. It is often considered that EPC is a form of focal cortical myoclonus, although subcortical mechanisms have also been proposed [31]. It has been related to fixed or progressive lesions involving the motor strip. Various inflammatory and immune-mediated diseases of the central nervous system may cause EPC, including in children [32]. The most typical is Rasmussen's encephalitis [33], but less frequent conditions, such as subacute sclerosing panencephalitis, should be considered, depending on the context [34].

Treatment and Prognosis

The various "standard" therapeutic recommendations for convulsive SE apply for clonic SE. In addition, EPC in the context of Rasmussen's encephalitis may respond to various protocols of steroid treatment, including intravenous methylprednisolone and oral prednisone, as well as to intravenous immunoglobulins [35, 36]. Patients are frequently refractory, and may require surgical intervention [35, 37].

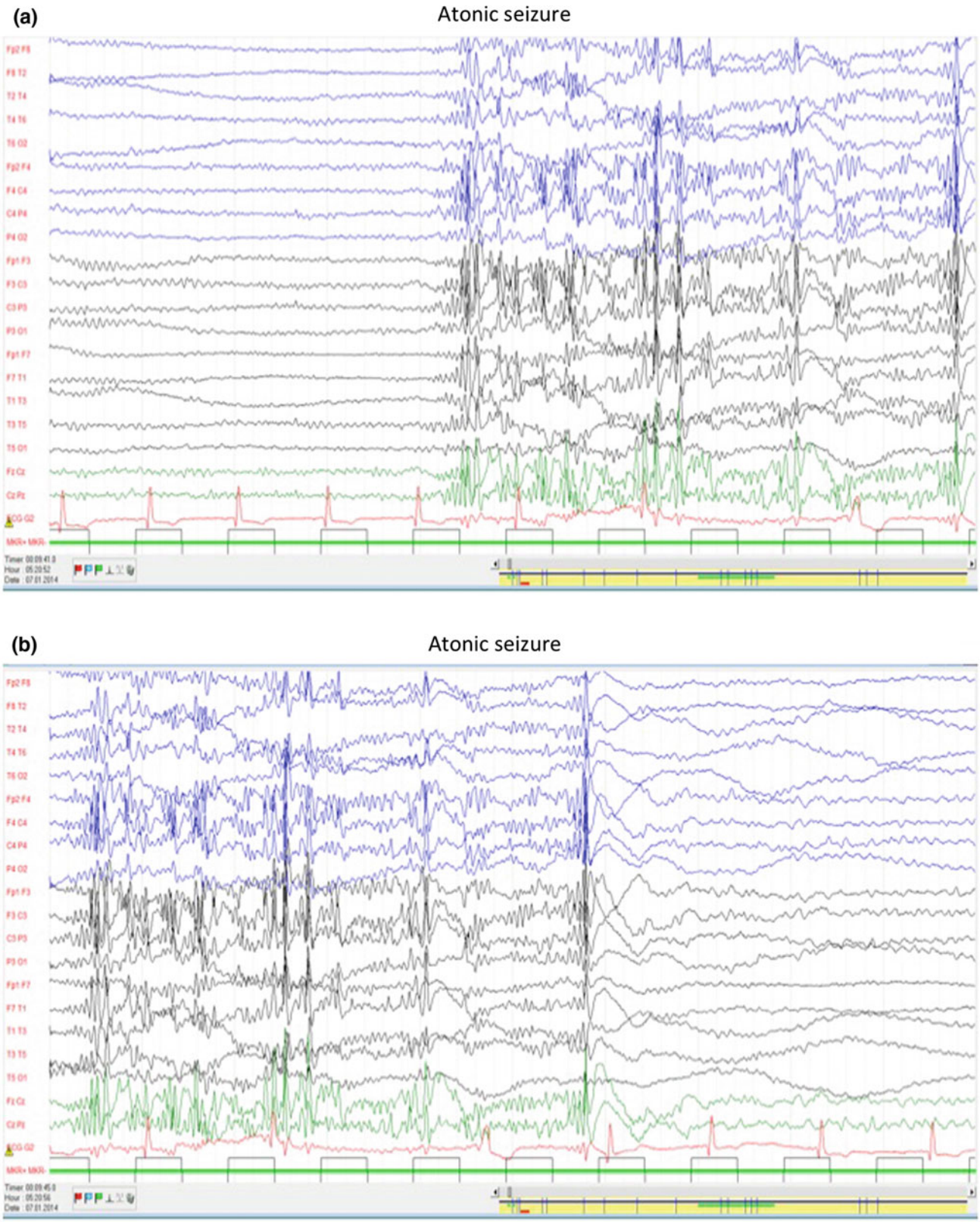

Fig. 14.1 Electroencephalogram (EEG) of a 38-year-old man with refractory epilepsy admitted for presurgical evaluation who presented with generalized tonic-clonic seizures and clusters of atonic seizures (repeated up to 60 times in an hour). Ictal EEG (bipolar montage, 70 mV/cm, 10 s) showed bifrontal rapid rhythms and synchronous bursts of bilateral polyspikes. Electromyography was not recorded. **a** Seizure onset, and **b** Termination of the seizure. (Image courtesy of Prof. Serge Vulliémoz, Neurology, University Hospitals, Geneva, Switzerland)

Atonic Status Epilpticus

Clinical Presentation and Context

Atonic SE is defined as prolonged or repeated episodes of atonic seizures characterized by partial or complete loss of muscle tone [22]. Clinical manifestations can be relatively subtle, with uprolling of the eyes, minor jerks, and partial disturbance of consciousness. The EEG typically shows bilateral synchronous spike and slow-wave activity [2]. Bifrontal rapid rhythms and synchronous bursts of bilateral polyspikes may be observed, as well (Fig. 14.1).

Atonic SE has been reported in patients with LGS but seems less common than nonconvulsive or TSE in that syndrome. It appears as "an inability to maintain the upright position, due to repetitive seizures or to serial head drops when the patient is sitting, without interictal clouding of consciousness" [4]. Two patients with discontinuous SE characterized by repetitive asymmetric atonic episodes associated with diffuse but asymmetric spike-waves have been reported in the literature [38]. Both patients had focal seizures and interictal rolandic discharges on EEG.

It should be noted that children with certain epilepsy syndromes might present with other types of prolonged seizures that mimic atonic SE, such as repeated atypical absences or nonconvulsive SE. An example is epilepsy with myoclonic astatic seizures, in which myoclonic, atonic/astatic, myoclonic astatic, and atypical absences may be observed and repeated long enough to suggest atonic SE [39]. These events are often difficult to diagnose, especially in children with intellectual disability, in whom impairment of consciousness and hypotonia are often attributed to other causes such as medication side effects.

Treatment and Prognosis

To our knowledge, no specific therapeutic approach exists for atonic SE [36]. Current recommendations for SE treatment in general likely also apply in this situation.

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Status Epilepticus in the Idiopathic Generalized Epilepsies

15

Michail Koutroumanidis

Introduction

Idiopathic Generalized Epilepsies (IGEs) comprise a group of epileptic syndromes that are genetically determined, unrelated to any structural brain pathology, and associated with normal neurological and neuropsychological status. The interictal electroencephalography (EEG) hallmark of the IGEs is the generalized spike-wave discharge (GSWD) at >2.5 Hz, occurring in association with normal background activity.

IGEs manifest with three main types of (primary) generalized seizure: typical absences (TA), myoclonic seizures (MS), and generalized tonic-clonic seizures (GTCS). Tonic and focal seizures are unusual. Therefore, status epilepticus (SE) in IGE (IGE-SE) is generalized and can take three forms, convulsive (IGE-GCSE), myoclonic (IGE-MSE), and absence status (IGE-AS).

In this chapter, we discuss all forms of IGE-SE across all IGE sub-syndromes in all age groups, the emergency EEG findings and the overall role of EEG in the diagnosis, and the differentiation of IGE-SE from other conditions that may present with similar clinical and overlapping EEG characteristics. In addition, the major epidemiological studies on SE are extensively reviewed to obtain a general sense of the possible frequency of IGE-SE. Concepts and definitions and the overall perspective combine (or are a compromise between) a clinically pragmatic stance in the emergency room and precepts of classical Epileptology in keeping with the 1989 International League Against Epilepsy (ILAE) classification [1]. Symptomatic causes of SE that may operate in patients with IGE (such as head trauma or intoxication) are beyond the scope of this chapter and are extensively reviewed in other sections of this book. We shall consider the existing evidence on other possible precipitants of IGE-SE that directly relate to their idiopathic nature, such as inappropriate anti-seizure drug treatment.

M. Koutroumanidis (✉)
Department of Clinical Neurophysiology and Epilepsies, St Thomas' Hospital, Guy's & St Thomas' NHS Foundation Trust, Westminster Bridge Road, London, SE1 7EH, UK
e-mail: michael.koutroumanidis@gstt.nhs.uk

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The Position of IGE-SE in the Recent ILAE Proposal on Definition and Classification of Status Epilepticus

The new classification framework is arranged along four axes [2]. On the **semiology** axis, IGE-GCSE is classified within the *generalized convulsive status* (A.I.a) group, together with other phenomenologically identical but etiologically different convulsive states. IGE-AS is classified as a distinctive type of *generalized NCSE without coma* (B.2.a.a—typical absence status), and IGE-MSE as another distinctive type of *generalized NCSE without coma (*B.2.a.c—myoclonic absence status). However, IGE-MSE may occur as a pure myoclonic state in clear consciousness, and as such may also be classifiable within the *myoclonic status without coma* (A.2.b) group, presumably together with other myoclonic states and epilepsies of different etiologies and prognoses (e.g., Dravet syndrome, and cryptogenic generalized or progressive myoclonic epilepsies).

In Axis 2 (*etiology*), the term "idiopathic" was not deemed applicable on the assumption that "*the cause of status is not the same as for the disease*" and treatment with inappropriate anti-seizure drugs was considered as one of the "*symptomatic*" causes, together with abrupt drug withdrawal, or drug intoxication. Nevertheless, inappropriate use of anti-seizure drugs (ASDs) does not feature amongst the main categories of the known symptomatic etiologies in the classification Appendix 1 of the proposal [2] (or in the 1993 ILAE guidelines [3]).

Treatment with inappropriate ASDs may indeed precipitate episodes of IGE-AS and IGE-MSE when they are first introduced, after dose increment, or even when used in a chronic regimen at a steady dose, but the mechanisms relate specifically to the very nature of IGE and do not operate in

symptomatic focal epilepsies. As discussed in the Pathophysiology section below, these agents increase the *innate* (idiopathic or genetically determined) *hyper*-excitability of the thalamocortical network through their GABAergic and "Na channel alignment" actions, *increasing the propensity* to seizures and by implication, the likelihood of seizure worsening and the occurrence of IGE-AS or IGE-MSE. Inappropriate ASDs do not cause SE in *all* patients with IGE [4] because the level of corticothalamic *hyper*-excitability is far from uniform among syndromes and even fluctuates in the individual patient. Episodes of IGE-AS can occur spontaneously [5–7] and as part of particular IGE syndromes, such absence status epilepticus (ASE) and epilepsy with phantom absences and absence status [8, 9], or as a late complication of long remitted IGE [10, 11]. Also, recurrent IGE-AS is seldom due to inappropriate treatment [7].

In Axis 3 (*electroencephalographic correlates*), IGE-AS and IGE-MSE have distinctive EEG profiles (namely > 2.5 Hz GSWD patterns), but there may be some overlap with other conditions, from which they should be differentiated. In Axis 4 (*age*), IGE-SE may affect patients of all ages from late childhood to the elderly.

Defining Time Frames for IGE-SE

The 2001 ILAE definition of SE as "*a seizure that shows no clinical signs of arresting after a duration encompassing the great majority of seizures of that type in most patients or recurrent seizures without interictal resumption of baseline central nervous system function*" [12] is in line with the original dictum that there are as many types of epileptic status as there are types of epileptic seizure [13] and essentially recognizes that the minimum duration of an epileptic seizure to be considered as status varies according to its type [14]. The time frame for GCSE is 5 min, as endorsed by the recent ILAE proposal (operational dimension 1) [2]. The same report proposes a time frame of 10–15 min for absence status, presumably associated with a continuous EEG pattern, but it provides no guidance about IGE-MSE [2].

It is certainly difficult to delineate EEG and clinical time frames for IGE-AS and IGE-MSE. Idiopathic absences are very brief seizures and become briefer and milder with age [15]. The classic form of IGE-AS is a prolonged absence associated with a more or less continuous SW discharges (Fig. 16.1), but forms with intermittent discharges of variable duration, repeated at short intervals as clusters of absences and with little tendency to cease spontaneously, are well known to exist [5, 16]. Similarly, IGE-MSE can occasionally be continuous and even regular, or take the form of sequential volleys at intervals of several seconds. Dense, discontinuous forms of IGE-AS and IGE-MSE can disrupt attention and culminate in GTCS, implying a common pathophysiological mechanism that facilitates and perpetuates epileptic discharges despite an apparent resumption of the electroclinical baseline, a non-fortuitous "fixed and lasting" condition [17].

Definitions of Concepts and Terms

Absence Status in IGE (IGE-AS)

Absence status in IGE is a state of variably altered consciousness, observable or subjectively perceived, which occurs in patients with IGE and is associated with continuous or intermittent 2.5 Hz or faster GSW EEG activity, irrespective of whether normal biological activity resumes in between the individual absences or the EEG paroxysms. The minimum duration matters less than in convulsive status and probably is not longer than a few minutes for continuous GSWD patterns, but significantly longer for discontinuous patterns.

Generalized Myoclonic Status in IGE (IGE-MSE)

Generalized myoclonic status in IGE is a state of intermittent, irregular and less frequently regular, bilateral myoclonic jerks of the limbs and head, or bilateral regional eyelid or perioral twitching, occur in patients with IGE. They are associated with bursts of fast-generalized polyspike-wave discharges (GPSWD) on EEG. Consciousness is preserved in pure IGE-MSE (although concentration and thinking may be fleetingly disrupted during prolonged and violent jerks) and variably clouded in mixed myoclonic-absence states; the latter are associated with mixed EEG patterns, as in IGE-AS with interspersed bursts of GPSWD with myoclonus.

Generalized Convulsive (Tonic-Clonic) Status in IGE (IGE-GCSE)

Generalized convulsive status is defined as GTCS lasting for more than 5 min [2] or repeated seizures over a period of more than 30 min without intervening recovery of consciousness [18]. Clinical distinction between the far more frequent symptomatic GCSE and IGE-GCSE is impossible, even when seizures are observed from the onset (symptomatic seizures may show bilateral synchronous onset, and "idiopathic" seizures may have initial focal signs), while the use and diagnostic yield of emergency EEG are also limited (see EEG section below). Diagnosis of IGE-GCSE is possible after the resolution of the status, by excluding symptomatic causes in a patient with an established diagnosis of IGE.

Epidemiology of Idiopathic Generalized SE (IGE-SE)

Extracting data about the incidence of IGE-SE from the major epidemiological studies is hampered, mainly by the conceptually different use of the term "*etiology"* to denote the *primary identifiable cause* of SE.

Most epidemiological studies have followed the 1993 ILAE guidelines [3], in which IGE is defined according to the 1989 ILAE classification [1], under the heading of "unprovoked seizures of unknown etiology." The terms "idiopathic" and "unknown" have been used interchangeably and, as a consequence, IGE-SE has almost invariably been classified within the "unknown" etiological category of SE without further diagnostic refinement.

In the prospective population-based Richmond Virginia study [19], "*idiopathic etiology*" comprised all SE that were *not* associated with identifiable acute or remote cause for the initiation of status. This presumably also included patients with cryptogenic or symptomatic focal epilepsies associated with mesial temporal sclerosis or focal cortical dysplasia that did not feature in the "remote symptomatic etiology." "Idiopathic" SE accounted for about 5% of childhood SE (presumably including idiopathic focal epilepsies of childhood) and 3% of SE in adults [19]. Similarly, in the population-based Rochester, Minnesota study [20] the incidence of IGE-SE appears low (possibly around 3%), while in a German study [21] the frequency of SE of "*unknown*" etiology reached 8.7% (13/150 of the total patients; no further data were available). In a hospital-based Bologna study [22] IGE-SE was classified together with cryptogenic SE, reaching a combined incidence of 7%. A notable exception was the Swiss EPISTAR study, in which accurate etiologic/syndrome classification showed that IGE-SE accounted for 1.75% (3/172) of all cases with SE and for 4% (3/74) of patients with SE and known epilepsies [23].

Seizure classification, another primary outcome measure, provides no useful information about IGE-SE, and can be even misleading. The percentage of GTCS as the *onset seizure type*, sometimes confusingly labeled as "*primary generalized*" [21], is typically much higher than the percentage given in the same report for the SE of "idiopathic etiology," ranging from around two-fold [21, 22] to 10-fold [19]. This discrepancy reflects underestimation of secondary GCSE rather than a higher incidence of IGE-SE; reasons include rapid secondary generalization, missing information about the onset of the GCSE, and the generally significant under-ascertainment rate that is higher in rural centers.

Definition of epilepsy type and its etiology (including IGE) is possible only in SE patients with a previous diagnosis of epilepsy, frequently requiring *post-status* clinical and EEG follow up, neither of which is amongst the primary objectives of epidemiological studies on SE.

IGE-GCSE

Considering the above limitations, information about IGE-GCSE has to rely on well-validated studies with EEG documentation. Earlier hospital-based studies concurred that GCSE was *never* the initial manifestation of IGE [24–26]. In his study on GCSE in patients with known epilepsy, Janz [24] found that the incidence was 6 times higher in symptomatic than in idiopathic cases, although the latter still accounted for almost a third of the total cases (30/95); a quarter of these patients had seizures on awakening, and one fifth had "diffuse grand mal epilepsies". The 1971 Oxford study found that GCSE was a late manifestation in 20 patients with constitutional epilepsy (23% of the total study population of 80), associated in *almost all* cases with GSWD and therefore well-validated IGE. All but one had good outcomes, and 7/20 had a family history of epilepsy. In that study, patients with GCSE in the acute phase of severe head injury had been excluded [25]. No specific cause for the GCSE could be found in 15% of the 98 patients of Aminoff and Simon [26] with presumed "primary" (constitutional) generalized epilepsy". Comparison between these hospital-based studies and the large population-based series is impossible, but one gets the impression that the incidence of IGE-GCSE has declined following the increasingly wider use of valproic acid (VPA) [27]. In a relatively recent EEG-assisted hospital-based study on patients with SE and known epilepsy, only 3 of the 50 patients (6%) had IGE, of whom none had IGE-GCSE [28].

IGE-MSE and IGE-AS

There are only few reliable epidemiologic data on IGE-MSE, mainly because such patients may be either included in the "primary generalized type" of convulsive seizures [21] or classified together with those with post-anoxic encephalopathies [22]. In the EPISTAR study, IGE-MSE occurred in probably just one patient (0.6%), marked as generalized clonic [23]. In a single hospital-based study of 50 patients, IGE-MSE consisting of diffuse positive and negative myoclonic jerks occurred in one patient diagnosed with juvenile myoclonic epilepsy (JME) (2%) [28]. In a well-documented series of 23 patients with MSE, mostly due to anoxic insults, only one had IGE-MS; he was diagnosed with poorly controlled IGE and remained conscious during the myoclonic status [29].

Epidemiologic data are far more robust for IGE-AS, as diagnosis requires EEG confirmation, with the caveat that GSWD should not always be equated to IGE-AS. Shneker and Fountain [30] noticed acute medical causes in 1/3 of their patients with NCSE associated with GSWD and a similar mortality to those without GSWD. The remaining 2/3

were classified as "epilepsy" including post-GTCS and frontal lobe status, and as "cryptogenic etiology" (i.e., without history of epilepsy), presumably including also cases with de novo absence status of late onset [30].

Amongst the best documented population-based epidemiologic studies the incidence of IGE-AS ranges from 1–2 [19, 22, 23] to 6% [21]. In a hospital-based study IGE-AS occurred in 2 patients with juvenile absence epilepsy (JAE) (4%) [28].

The incidence of status in patients with IGE is known only for IGE-AS, ranging from 10 [16] to 25% when video-EEG is used [5].

Pathophysiology of IGE-SE and Some Clinical Considerations

It has been hypothesized that the alternating cycles of excitatory postsynaptic potentials (EPSPs) and inhibitory postsynaptic potentials (IPSPs) that generate both the regular synchronized 3–4 Hz GSWD discharge of typical absence seizures (and absence status) and sleep spindle oscillations, involve the same thalamocortical network, including the nucleus reticularis thalami (nRT), which is rich in GABAergic interneurons.

In GSWD, an abnormal longer burst (possibly from increased regional, but not steadily localized, cortical firing) [31] results in a 3-times longer IPSP that is mediated through GABA-B receptors (still at the nRT), effectively setting the frequency of the GSWD oscillation down to the familiar 3 Hz [32]. Such nonlocalizing cortical firing may relate to the frequently seen "focal non localizing spikes" on the scalp EEG of patients with IGE [33, 34]. The perpetuation of the 3–4 Hz GSW oscillations depends on calcium channels that first, deactivate during the slow depolarization of the thalamocortical cells (EPSP) and then, reactivate by the hyperpolarization of these neurons (during the IPSP) and open up, producing low-threshold calcium spikes that will trigger a burst of action potentials and lead to the next cycle of the thalamocortical oscillation [35].

Termination of the 3–4 Hz GSW oscillations has been hypothesized to involve an increase in intracellular calcium (Ca) (due to repetitive oscillations), leading to increased intracellular cAMP. This then blocks the hyperpolarization of the thalamocortical network and the reactivation of the Ca channels, and eventually the generation of low-threshold calcium spikes [36]. The relatively slight depolarization of thalamic neurons (rather than their depression or hyperpolarization) may explain the lack of postictal cognitive deficits [37].

Episodes of IGE-AS (and worsening of typical absences) can be facilitated by GABAergic drugs such as the GABA agonist baclofen, and the ASDs vigabatrin, [38, 39] and tiagabine [40], which are irreversible inhibitors of GABA transaminase. The reported pro-absence effects of carbamazepine and phenytoin [4, 6] appear two-fold: (1) they may facilitate de-inactivation of (i.e., activate) the low-threshold calcium spikes that perpetuate 3 Hz GSW oscillations [41], and (2) they increase the already innately enhanced tendency for oscillatory hypersynchrony through "Na channel alignment" [42].

On the other hand, the effectiveness of benzodiazepines (BDZ) in IGE-AS may relate to reduction of the GABA-B component of IPSPs and currents [43] and thereby, block Ca channel reactivation and the generation of calcium spikes, and hence eventually arrest the ongoing GSWD.

Age at IGE-SE Onset

Most reports concur that the first IGE-SE typically occurs in adulthood. In the London series, the first episode of IGE-AS occurred well after the onset of TA and GTCS (mean onset of IGE-AS: 29.5 years; TA: 9 years; GTCS: 21 years), although it appeared as the *first overt* clinical manifestation of IGE in up to 1/3 of patients [5]. Subsequent clinical and EEG follow up showed that these patients had epilepsy with phantom absences [44].

There exist only a few reports on IGE-AS in children younger than 10 years of age. IGE-AS has been mostly reported in young children with syndromes other than the classical childhood absence epilepsy (CAE), such as phantom absences [45], absence epilepsy with features atypical for CAE [7], perioral myoclonia with absences (POMA) [46], or eyelid myoclonia with absences (ELMA) [47]. In a large Japanese video-assisted EEG study, children with absence status had brief absences but also other types of generalized seizures, including astatic seizures; their absences were brief and described as "atypical," while half of them had features consistent with Lennox–Gastaut syndrome [48].

Sex Ratio

IGE-AS [5, 16] and mainly IGE-MSE [49, 50] appear to affect women more than men.

Precipitants and Recurrence

Precipitants for IGE-AS/IGE-MSE include sleep deprivation, excessive alcohol intake, fatigue, stress or relaxation, and withdrawal of (or noncompliance with) appropriate treatment. Febrile illnesses, surgery, or menstruation have also been reported [5, 51]. Episodes of IGE-AS/IGE-MSE

are well known to occur with the inappropriate use of sodium channel blocking ASDs in patients with IGE [4, 6, 52], during chronic treatment at a steady dose with these drugs [49, 52, 53] and with dose increments [52] or treatment initiation [40, 54–56]. In patients with IGE, such adverse effects cannot be considered as "paradoxical" or as symptomatic causes [2] (see also earlier sections on ILAE classification and pathophysiology).

Seizure Symptoms and Semiology

The fundamental disturbance in ASE is *clouding of consciousness*. This can vary from a mild, almost exclusively subjective perception of feeling unwell and not up one's usual personal baseline (imperceptible to others) to a clinically overt confusional state and less frequently, a severe psychomotor retardation or stupor. Minor fluctuations are reported by many patients, presumably reflecting clusters of absences. As a rule, they are less evident than the typical fluctuations of mental state in patients with CPSE [57], while gradual deterioration has been reported in up 20% of patients [5]. Descriptions of their own symptoms and ictal experiences by patients with mild clouding can be found elsewhere [58].

The degree of mental clouding determines the extent of impairment of other cognitive functions. Speech is usually reasonably preserved, in marked contrast to the true dysphasia of complex partial status epilepticus (CPSE), due to direct ictal invasion of speech centers. It may vary from mild slowness and poverty of content or fluency, to perseverative and monosyllabic speech. Amnesia is also variable and usually patchy (and only occasionally total), in contrast to the amnesia that characterizes CPSE [59]. In general, *behavior* slows down and patients become withdrawn, although occasionally agitation, irritability, or aggression can also occur [16, 59].

Motor phenomena include bilateral rhythmic blinking or small amplitude myoclonic jerking of the arms, automatisms, and pseudo-ataxic or hesitant gait. Facial (eyelid or perioral) myoclonus is typically similar to that in the typical absences in a given patient, conforming thus to the profile of the specific sub-syndrome or condition (e.g., eyelid or perioral myoclonia) [5, 7]. Complex automatisms or lateralized motor manifestations or stereotypes may occur when IGE-AS is precipitated by inappropriate ASDs [52]. Experiential phenomena and complex visual hallucinations or illusions are not infrequent [5, 7, 16, 60]. Excellent clinical descriptions of behavioral changes during IGE-AS can be found in the seminal paper of Andermann and Robb from 1972 [16].

Pure IGE-MSE typically occurs in patients with JME and consists of clusters of arrhythmic bilateral myoclonic jerks of the limbs or head or both, in the absence of clear impairment of consciousness.

IGE-AS episodes may last for several minutes to days [5, 7, 16]. Because IGE-AS usually responds well to appropriate treatment, long duration usually reflects underdiagnosis or misdiagnosis of the condition. A 6-weeks-long IGE-AS was documented in a 66-year-old man, in whom sub-therapeutic levels of VPA (due to co-medication with phenytoin) and chronic white matter ischemic changes were thought to sustain the state [61]. Because of its conspicuous clinical presentation, IGE-MSE is diagnosed and treated earlier.

Electroencephalography (EEG): The Two Phases of EEG Diagnosis

Emergency *ictal* EEG is diagnostic and can effectively guide acute treatment and short-term management. In newly presented patients and after the resolution of the status episode, *interictal* video-EEG studies can consolidate the diagnosis of IGE by showing 3 Hz GSWD with a normal background, and optimally used [62], may refine syndrome classification and assist long-term management and prognosis. In patients with a history of epilepsy, reports of earlier EEGs (and actual traces if possible) are worth pursuing as they may contain important diagnostic clues that are no longer present.

In patients presenting to the emergency department with serial GTCS, emergency ictal or peri-ictal EEG may reliably indicate secondary generalization by demonstrating regional electrographic onset or lateralized postictal suppression, prompting urgent search for the focal symptomatic cause. Nevertheless, the absence of focal EEG changes is *not* diagnostic of IGE. Electrocerebral suppression in the early postictal phase can also exclude non-epileptic psychogenic status and prevent iatrogenic morbidity from aggressive emergency anti-seizure treatment and forestall admission to an intensive care unit [63, 64]. Emergency EEG may also detect NCSE in patients with unusually prolonged "postictal confusion." In extreme circumstances (for instance in agitated patients), a limited number of EEG electrodes may suffice insofar as frontal (Fp1, Fp2), temporal and occipital electrodes are placed, including a midline electrode (Fz or Cz) that is the least affected by muscle activity. Concurrent electromyogram (EMG) may provide invaluable information in the case of intermittent motor activity, while video monitoring (which is no substitute for EMG polygraphy) and ECG monitoring are essential.

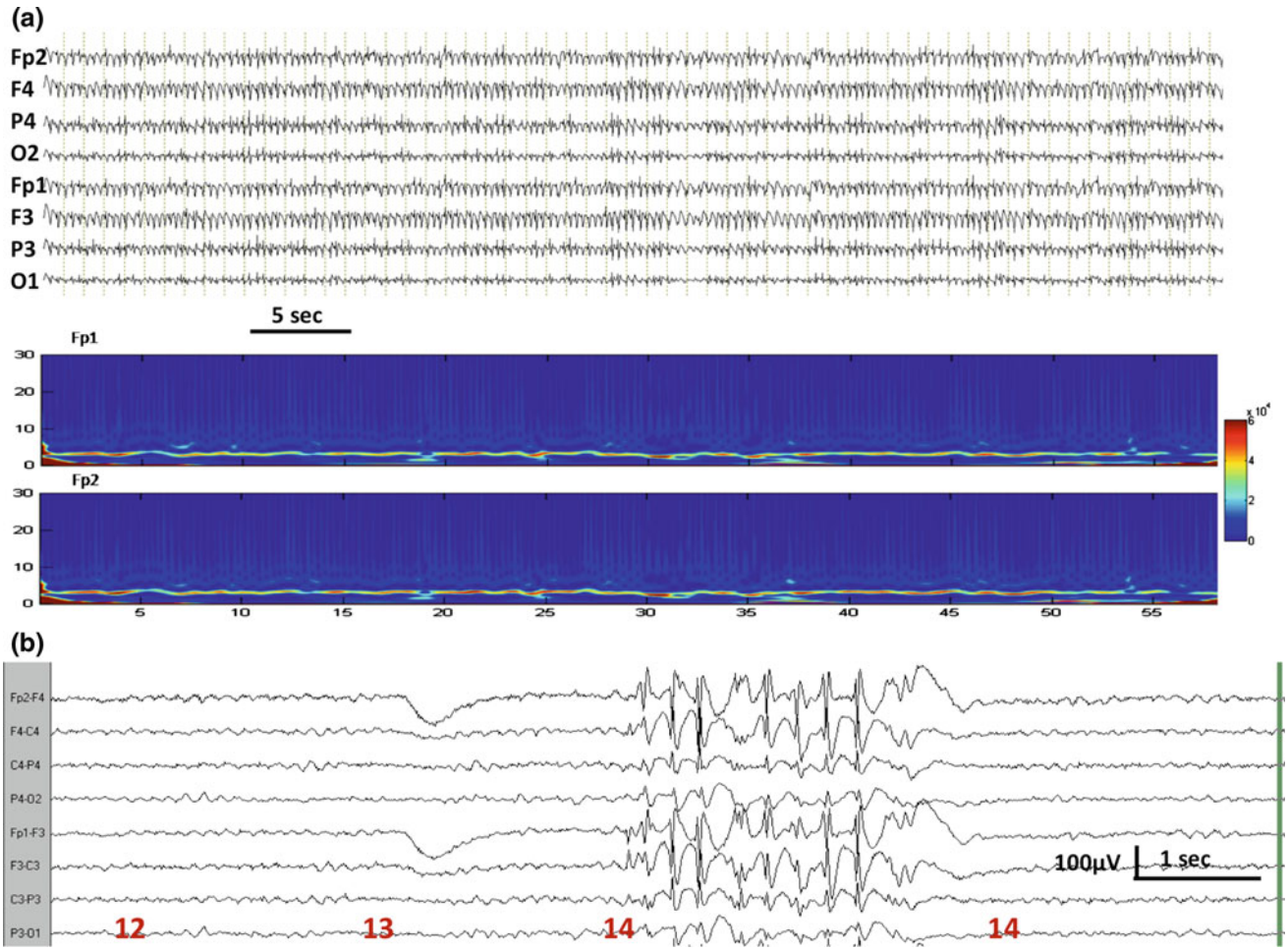

Fig. 15.1 **a** Electroencephalogram (*EEG*) with time-frequency analysis (*TFA*) on a 58-year-old woman with about 35 generalized tonic-clonic seizures since the age of 30 years. This patient is in IGE-AS with moderate clouding of consciousness but fully ambulatory. The status was resistant to IV benzodiazepines and was treated successfully with IV valproic acid. **b** Diagnostic video-EEG after the resolution of the status, showing hyperventilation with the patient counting each breath. Note the hesitation caused by the 2 s generalized spike-wave discharge (phantom absence). She had no prior history of absences, and no absences were recorded in video-EEGs, other than phantom absences. The patient had been treated with carbamazepine (*CBZ*) for a number of years and became seizure free when CBZ was replaced by valproic acid

Emergency video-EEG recordings are far more useful in patients with suspected NCSE and should always be pursued as soon as possible [65]. Diagnosis of IGE-AS/IGE-MSE and their differentiation from CPSE, de novo absence status of late onset, and non-epileptic states is based on the recognition of the 3 Hz GSWD, bearing in mind that in late stages of idiopathic AS, spike-wave frequency may drop below 2.5 Hz, and morphology may change (see respective sections).

In IGE-AS/IGE-MSE there is usually a rapid clinical or EEG response or both following intravenous (IV) benzodiazepines (BZDs), whereas a more gradual improvement would suggest another cause, even with a deceptively similar EEG picture, such as in some forms of frontal lobe status [66]. Notable exceptions may include IGE-AS that can be proven particularly resistant to IV VPA or BZD when associated with the use of inappropriate ASDs such as carbamazepine (CBZ) or PHT [6].

Ictal EEG patterns consistent with the diagnosis of IGE-AS may include any continuous (Figs. 15.1, 15.2, and 15.3) or discontinuous, rhythmic or arrhythmic at the equivalent frequency of around 3 Hz GSWD patterns; slower repetition rates interspersed with slow waves may occur in late stages of the AS state [61] when discharges become increasingly irregular (Fig. 15.4), as in some patients with IGE-AS precipitated by inappropriate ASD treatment [52].

IGE-MSE, as in JME, is characterized by fast (>3–4 Hz) irregular arrhythmic GPSWD that typically correlate with bilateral myoclonic jerks when EMG polygraphy is

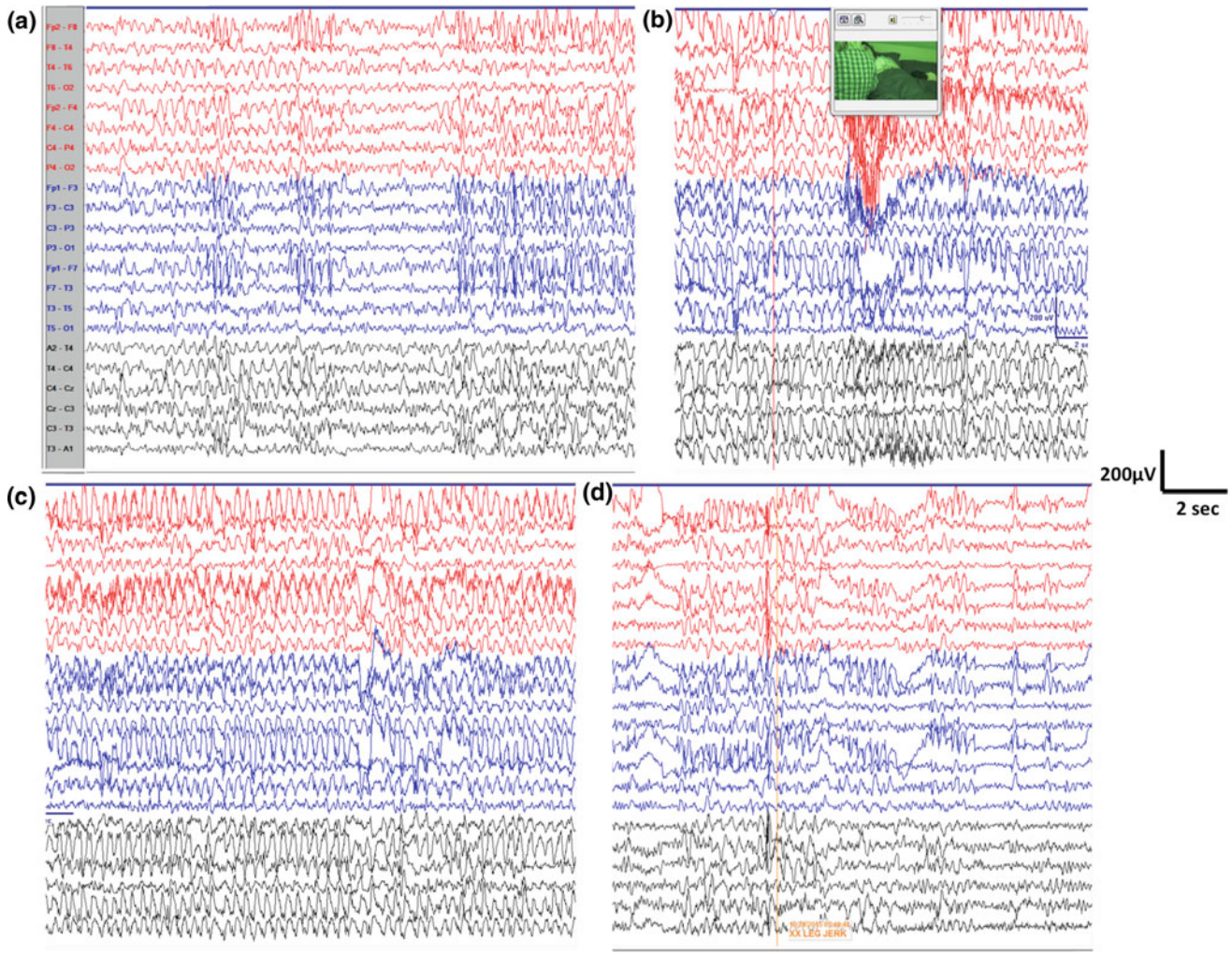

Fig. 15.2 Idiopathic generalized epilepsy absence status (IGE-AS) associated with continuous >2.5 generalized spike-wave discharge (*GSWD*) in a 30-year-old woman with absences since the age of 7 years and generalized tonic-clonic seizures since her teens (3-day long home video-telemetry). The test recorded a small number of mild fleeting absences and a 34 min long episode of AS that was not associated with clinically overt behavioral changes or symptoms that would prompt her to activate the event marker. During the AS episode, she mostly remained in her bed, but she also got up to go to the bathroom, taking the electroencephalogram head box with her, and had a sensible conversation with her mother, without either of them signaling that something was wrong. Consciousness was more affected in other episodes of IGE-AS with the patient not being able to finish sentences, giving the wrong answers to simple questions, perseverating with her speech and feeling "wobbly," and having twitches in her body, with her eyes "wandering off." **a** Onset of AS at 7:16 AM after some clusters of GSWD (discharges became continuous thereafter). **b, c** At 7:41 AM. **d** Spontaneous termination of AS at 7:49 AM. Traces (**b**) and (**c**) are continuous

employed. Background rhythms in between the GPSWD are normal unless MS are too dense or the epileptic state is punctuated by GTCS.

Video-EEG during absence status in ELMA typically shows repetitive (every 2–4 s) generalized discharges of polyspikes and polyspike waves, associated with marked eyelid myoclonia. The flicker effect of the protracted eyelid jerking or tonic contraction and the associated upward movement of the eyes (Evans–Mulholland effect) may kindle spike-wave discharges resulting in sustained eyelid myoclonia. In this case, patients may appear unable to maintain eye opening for several seconds at a time. When they finally do manage to hold their eyes open, discharges may block, with EEG normalization, only until the next eye closure, triggering a new cluster of eyelid myoclonia. Therefore, the electrographic pattern of AS is essentially discontinuous, with brief epochs of normal activity. High epileptic pressure associated with almost continuous discharges and intense eyelid myoclonia may impede eye opening for long periods and result in a continuous EEG pattern [54].

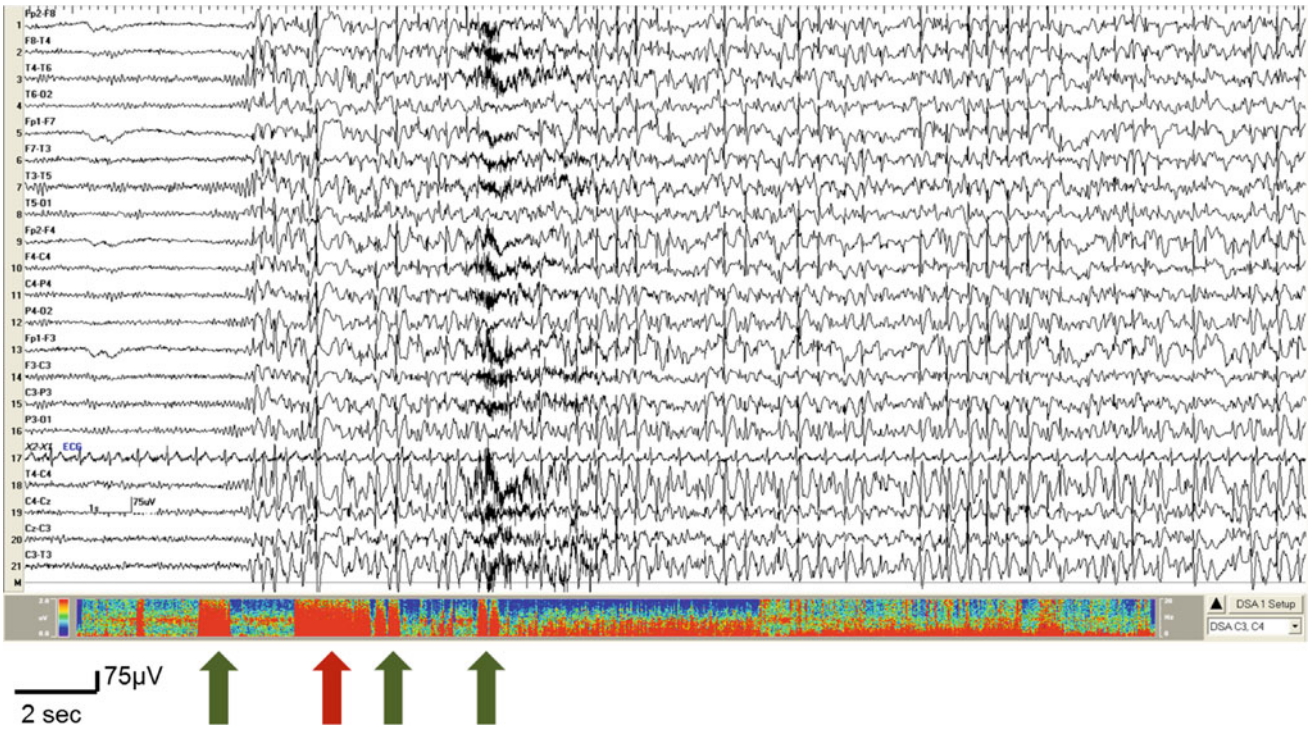

Fig. 15.3 Absence status epilepsy (*ASE*). First diagnostic video-electroencephalogram on the patient of Fig. 15.6 when she was referred with 3 generalized tonic-clonic seizures at the age of 47 years; she had been on carbamazepine. This is the onset of an 8-min episode of *continuous* generalized SW activity at 3 Hz, during which she remained quiet, with her eyes semi-open and mild eyelid flickering (*red arrow* in the density spectral array (*DSA*) graph at the *bottom* of the figure). All episodes (shown also by *green arrows*) occurred spontaneously and would promptly terminate as soon as the technologist spoke to her. ASE episodes became less frequent and milder after her treatment was changed to valproic acid, but continued to occur

Nonconvulsive (Absence and Myoclonic) Status in Individual IGE Syndromes

Juvenile Myoclonic Epilepsy (JME)

Episodes of IGE-AS/IGE-MSE appear to be rare in JME. Three studies on JME patients examined status and included about half of the total published cases of status in this syndrome [5, 49, 50]; the rest were presented as case reports, while larger series have focused on the effect of treatment with ASDs inappropriate for IGE [6, 52].

Agathonikou et al. [5] reported IGE-AS/IGE-MSE in 2 of their 30 JME patients over 5 years (6.7%); Dziewas et al. [49] in 4 of their 69 patients (5.8%) over a similar period; and Larch et al. [50] in 7 of their 247 patients over 37 years (3%).

Clinically, a dominant myoclonic component characterizes the majority of the reported cases. Clinical descriptions are available for 25 patients, indicating 3 clinical forms, IGE-MSE, IGE-AS, and mixed IGE-AS/IGE-MSE. Pure IGE-MSE has been clearly described in 8 patients. It is characterized by arrhythmic bilateral myoclonic jerks of the head, limbs, or both, either continuous every few seconds, or in clusters every 10–15 s, *in the absence of clear impairment of consciousness,* or other symptoms. A notable exception was the patient reported by Badhwar et al. [53], who reported an overwhelming feeling of needing to void. In two patients with a diagnosis of JME, myoclonus was restricted to the ocular muscles, preventing eye opening [52, 54]. Mixed episodes were described in 13 patients, typically as states of confusion with superimposed bilateral jerks, mainly of the upper limbs. Boundaries between these two types are not always clear, and in some patients periods of lapses of attention or staring spells may alternate with periods with predominant myoclonic jerks [67]. IGE-AS associated with mild infrequent eyelid blinking, but not with limb jerking, is the rarest type, reported only in four patients. The age at the first status episode ranges from 10 to 69 years and was between 20 and 35 in half. An episode of status was never the *first* presentation of the JME in any of the patients. Even in patients with apparently de novo IGE-AS status, careful history taking after the resolution of the state reveals earlier myoclonic jerks that had passed unnoticed, or had never been appreciated as "abnormal" by the patients [68]. Women outnumber men (ratio 4:1 in patients with known gender).

Myoclonic and absence-myoclonic status episodes can occur spontaneously during the course of the disease in drug-naïve

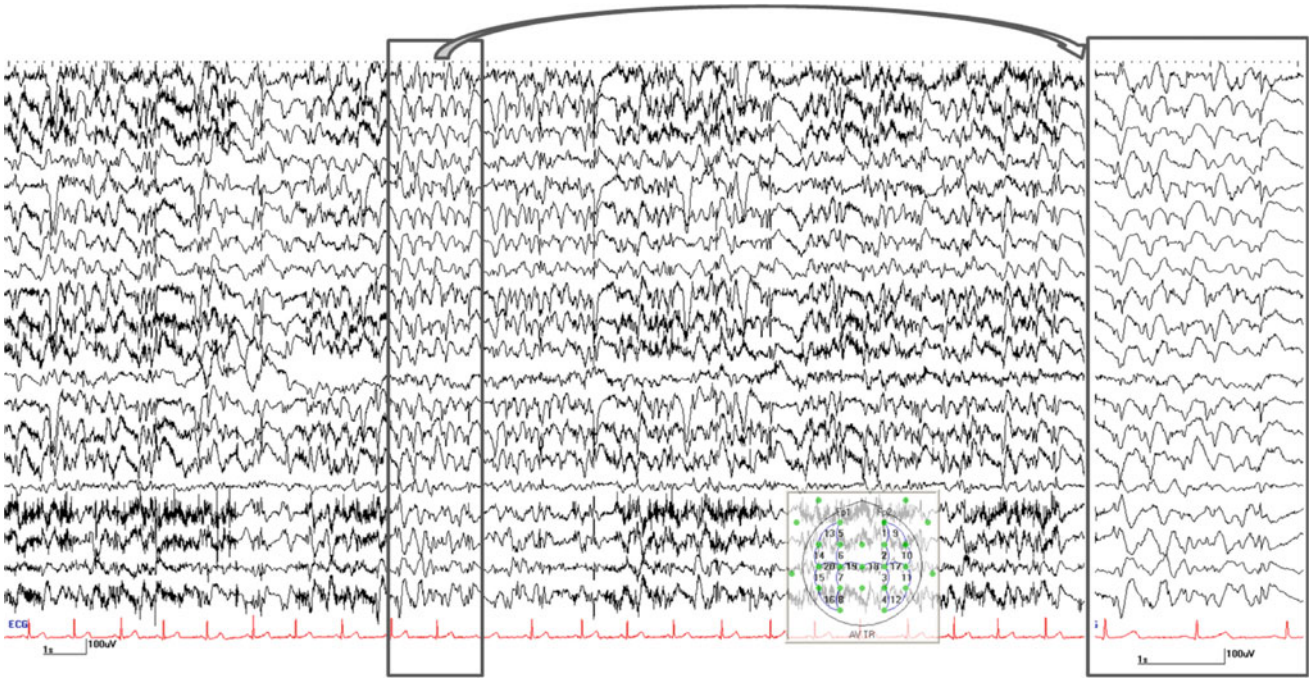

Fig. 15.4 Electroencephalogram (*EEG*) showing idiopathic generalized epilepsy absence status in a 59-year-old woman with frequent attendances to the Emergency Department for episodes of prolonged confusion. Throughout this EEG, performed several hours after the onset of the status, she remained in a sitting position with her eyes open. She was unresponsive to commands, though she seemed vaguely aware of the presence of people around her. She had some semi-purposeful movements and at times, slight shaking of the hands and feet. Note the arrhythmic continuous pattern of the generalized discharge, the frequency of which ranges from ≤ 2 to 4 Hz

patients [68] (Fig. 15.5), often precipitated by sleep deprivation, tiredness, stress. The same factors, and in addition ASD withdrawal or poor compliance, can precipitate absence / myoclonic status in already treated patients. Further, the literature contains ample evidence that inappropriate for IGE anti-seizure drugs, either in chronic therapy or after dose increment or add-on treatment, can facilitate or trigger episodes of absence / myoclonic status [4, 6, 52–54, 56, 67]; IGE-GCSE induced by inappropriate ASDs appears sparse [6]. A more complete picture emerges from the three large series [5, 49, 50] with 13 patients with absence / myoclonic status among them: 2 had spontaneous episodes, 4 had episodes after ASD withdrawal, 6 had been on chronic treatment with inappropriate ASDs, and one had a single episode induced by vigabatrin. It is also noted that in a minority of JME patients recurrent unprovoked episodes of status may occur despite appropriate treatment, possibly suggesting a rare spontaneous adverse evolution of an earlier-benign course [5, 7].

Differentiation of IGE-MSE from non-epileptic myoclonic states mimicking JME *requires* emergency EEG to confirm the absence of any GSWD in association with the myoclonic jerks. It is emphasized that interictal EEGs may be normal in some patients with active JME. Non-epileptic MSE can be clinically suspected when adequate appropriate treatment has been ineffective and there is evidence of a psychiatric disorder [69].

Juvenile Absence Epilepsy (JAE)

The reported frequency of IGE-AS in JAE is higher than that in JME, but it varies widely among different studies (3.2% [70], 20% [5], 27.4% [71], and 38% [72]), presumably owing to different diagnostic criteria. Concurrent myoclonic jerks occur infrequently and do not dominate the clinical picture. Episodes may occur spontaneously, facilitated by sleep deprivation and menstruation [5] but can also be induced by inappropriate ASDs for IGE [55] or be related to chronic treatment with CBZ and PHT, including during dose increments [52]; 7 of the 8 patients with inappropriate ASD-induced ASE were women.

Eyelid Myoclonia with Absences (ELMA)

IGE-AS episodes are characterized by sub-continuous eyelid myoclonia with upward eye deviation and mild to moderately severe impairment of consciousness. Patients with intense eyelid myoclonia may appear unable to open their eyes to command (see EEG section above). Agathonikou et al. [5] reported absence status in 2 of their 11 patients (18.2%) over 5 years, while Smith [73] reported absence status in 3 of the 5 patients seen at the Chalfont epilepsy center over 3 years. The age at first episode of absence status has ranged from 8 to

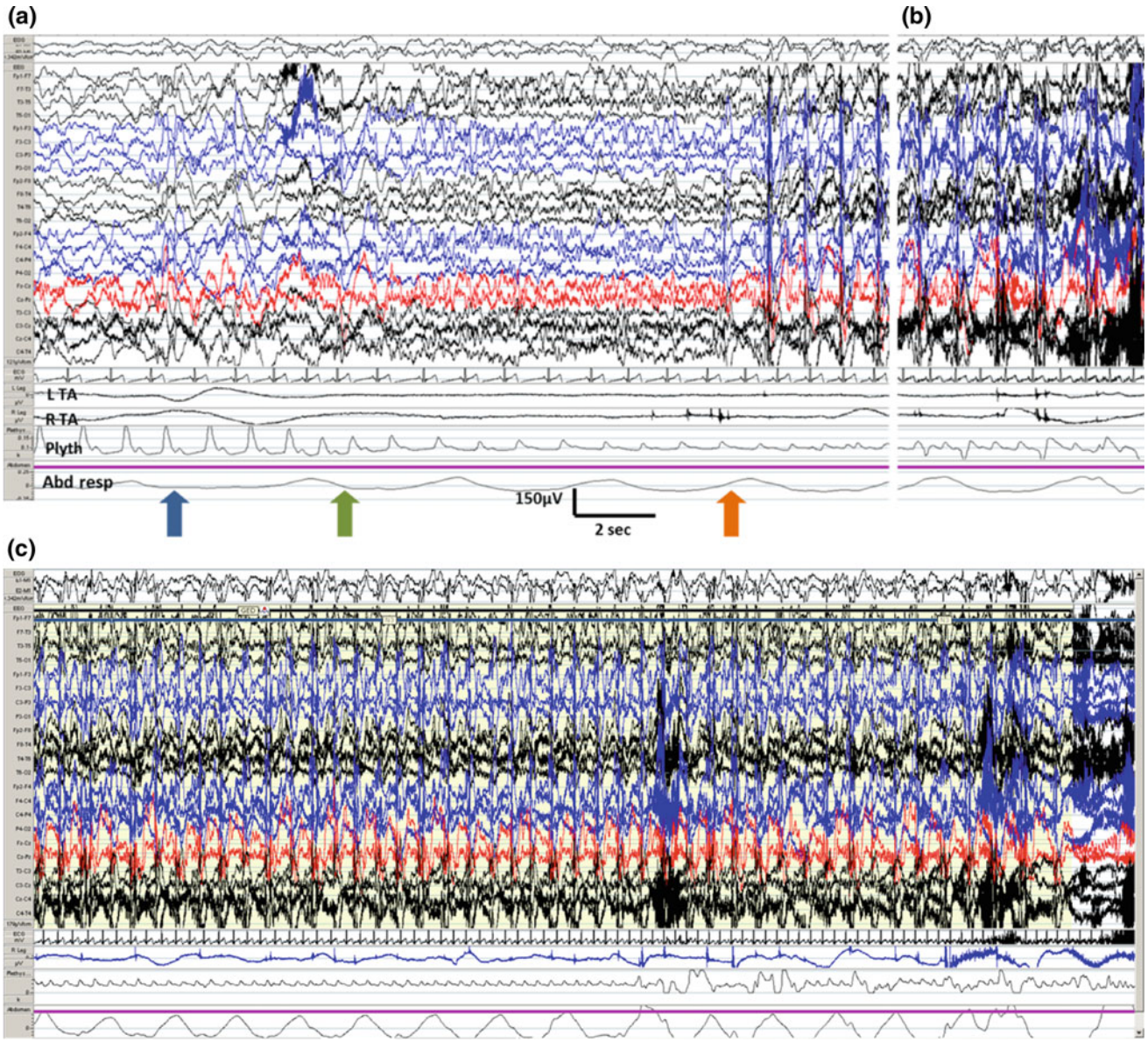

Fig. 15.5 Myoclonic status epilepticus (*MSE*) in a 19-year-old man with drug-naïve JME, apparently arising from deep sleep. Note the spontaneous high voltage delta arousal from stage 3 of sleep (*blue arrow*), followed by the appearance of faster rhythms and emergence of alpha activity (*green arrow*) that precedes the first GPSWD (*orange arrow*). In contrast to what the apparent behavioral changes (and patient's own account) would suggest, MSE actually occurred upon awakening (following a spontaneous arousal) and not from sleep. Also, note the regular pattern of the IGE-MSE. The patient remained conscious throughout the IGE-MSE, which did not evolve into a generalized tonic-clonic seizure

27 years. Liability to absence status is maximal in the morning after awakening. All reports indicate that episodes are typically precipitated by eye closure in bright sunlight, but exceptionally they can also occur in total darkness after clinical photosensitivity has been controlled by medication [47]. Episodes have also occurred during severe infections [7, 73] and after withdrawal of ASDs [5]. They primarily affect women (10:1) and show a strong tendency to recur. In two patients, absence episodes were associated with headache, resulting in a misdiagnosis of migraine attacks [7, 74].

Perioral Myoclonia with Absences (POMA)

POMA is a rare form of IGE, in which typical absences are characterized by rhythmic contractions of the perioral

musculature. GTCS occur in all patients and episodes of IGE-AS in more than 50% of them, starting at any age and with a strong tendency to recur [5]. As the typical absences in this syndrome, IGE-AS is frequently characterized by oral or bulbar myoclonus that can be intense enough to cause marked dysarthria [46] or impede drinking and eating [75]. POMA appears to be rare, but as *all* reports have pointed out, it is frequently misdiagnosed as focal epilepsy [46, 75–77], including *epilepsia partialis continua* in one patient with lateralized oral twitching [78]. Correct diagnosis requires demonstration of the characteristic IGE features, including typical absences (found most readily by video-EEG with hyperventilation [HV] on awakening) *after* the resolution of the AS.

Absence Status Epilepsy (ASE)

As the term indicates, ASE is characterized by recurrent, unprovoked episodes of IGE-AS, which is the predominant and defining seizure type for this syndrome (Figs. 15.3 and 15.6). Most patients have infrequent GTCS, while a few have a history of (also infrequent) absences but cannot be classified into childhood or JAE. Phantom absences and MS are not part of this syndrome, and photosensitivity has not been reported (Table 15.1]. As in the epilepsy with phantom absences, episodes of IGE-AS occur without provocation and are not merely due to the aggravating effects of inappropriate ASDs used in IGE [8, 79].

Idiopathic Generalized Epilepsy with Phantom Absences (E-PA)

The typical presentation of E-PA is the adult with the first GTCS or with an episode of IGE-AS, usually culminating in a GTCS. There is no earlier history of absences or myoclonic jerks, including in childhood or early adolescence. Diagnostic video-EEG *after* the IGE-AS shows brief 3–4 Hz GSWD associated with brief hesitations, omissions or repetitions of a reciting number during HV with breath counting, or a fleeting motor arrest reflecting impaired concentration, motor execution, or both (PA) (see Fig. 15.1) [80]. PA is the *defining* seizure type; conventional TA and MS are not part of E-PA. Because of the clinical imperceptiveness, the age of onset of PA cannot be ascertained, so the onset of E-PA is defined by the first overt clinical manifestation, either a GTCS or an episode of IGE-AS.

All patients have GTCS, and half may have one or more episodes of IGE-AS (see Fig. 15.1), but the latter does not

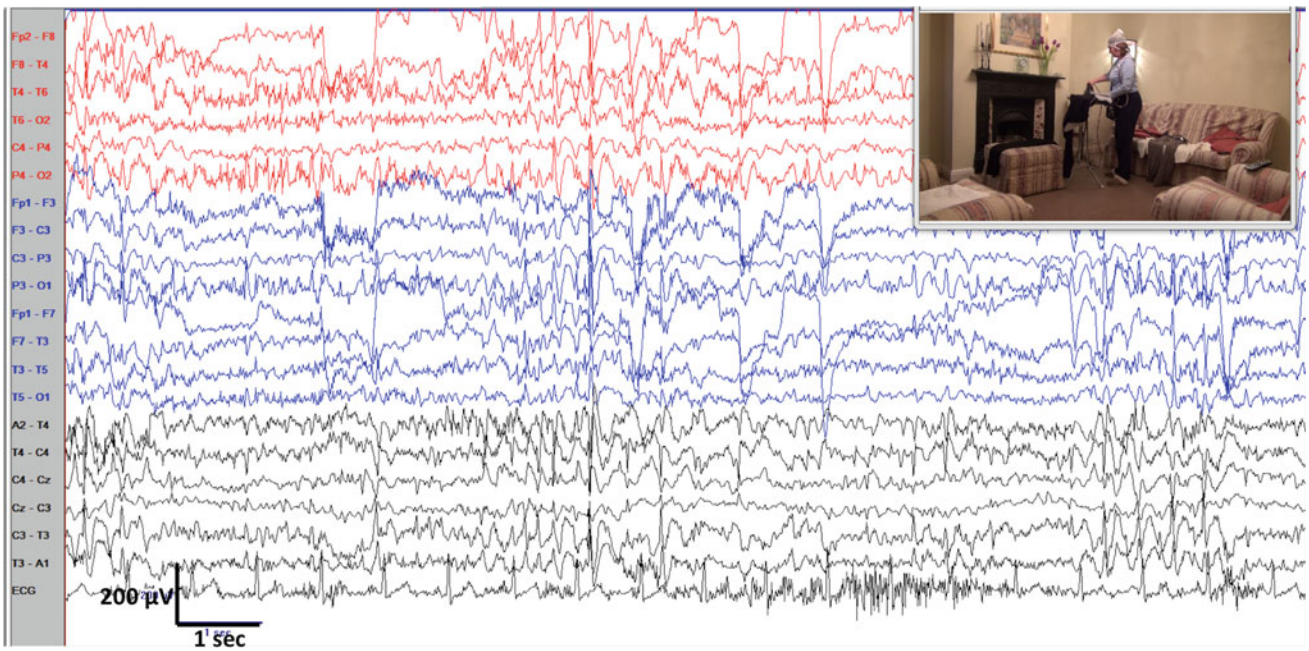

Fig. 15.6 Home video-telemetry on a 50-year-old woman with monthly episodes of absence status, probably since her early 20 s. She had infrequent absences as a child, and 4 generalized tonic-clonic seizures in total, the first at age 17 and three within one month at age 47. Note that the pattern is discontinuous and arrhythmic. She was able to perform all her usual activities at home (here she is ironing), including socializing with relatives in the evening, apparently without any undue behavioral changes. On other occasions, however, she reported mild difficulty in maintaining concentration

Table 15.1 Absence status epilepsy (ASE) and epilepsy with phantom absences (E-PA)

	ASE	E-PA
Age at onset	Adolescence to early-mid adulthood	Adolescence to mid-adulthood; typically peaks in early adulthood[a]
GTCS	In most patients	In most patients
Circadian distribution of GTCS	Before noon (AM), but may vary (interspersing or concluding ASE)	Before noon (AM), but may vary (interspersing or concluding ASE)
Absence status (ASE)	*Defining seizure type*	In up to 50% (variable frequency)
Phantom absences[b]	Not reported	*Defining seizure type*
Absences	Infrequent[c]	Exclusion criterion
Myoclonic seizures	Not reported	Exclusion criterion
PPR	Not reported	Infrequent

[a]Refers to the first GTCS or episode of absence status, as the age at PA onset is by definition impossible to ascertain
[b]Diagnosed only by video electroencephalogram (see text)
[c]Not classifiable as either childhood or juvenile absence epilepsy
GTCS generalized tonic-clonic seizures, *PPR* photoparoxysmal response

dominate the clinical presentation as in the syndrome of ASE. Episodes of IGE-AS were associated with inappropriate use of particular ASDs in the treatment of 6 of 16 patients in three reports [5, 7, 9, 44], but a clear precipitating ASD effect was seen in only one patient.

IGE-AS Associated with Fixation-off Sensitivity (FOS) and Eye Closure Sensitivity

Fixation-off sensitivity (FOS) is the occurrence of epileptic EEG discharges upon elimination of visual fixation [81]. FOS is infrequently associated with seizures, but there is a handful of well-documented cases of women with periodic episodes of IGE-AS associated with eyelid myoclonus and sometimes with GTCS [51, 82–84]. EEG during status showed attenuation or elimination of GSWD by visual fixation, and interictal EEG confirmed FOS without photosensitivity. Episodes were catamenial in three patients and periodic, every 2 weeks, in the fourth [82]. The threshold of FOS is expected to fluctuate in the same patient and, although the clinical picture may develop over time, these cases may constitute a pure form of FOS IGE [84].

Reports of patients with episodes of IGE-AS triggered by eye closure *outside* the syndrome of ELMA are sparse. A 44-year-old woman was described recently with catamenial IGE-AS, characterized by inability to maintain her eyes open, distractibility and macropsia, and associated with eye closure sensitivity but not with photosensitivity or FOS [85]. Her IGE-AS episodes started in childhood, and there were striking similarities to the case of a girl with JME reported by Kimura and Kobayashi [54]. The mechanism of discharge generation is similar to that in ELMA but without the added effect of photosensitivity (see ELMA and EEG section).

Diagnosis

All major studies agree that there is a high rate of misdiagnosis and underdiagnosis of SE in the IGEs [5, 7, 16, 52]. Reasons for this substantial diagnostic failure include the considerable clinical overlap between CPSE and IGE-AS, and the subtlety of the clinical manifestations in a substantial number of patients with IGE-AS episodes. Misdiagnosis arguably also reflects the frequently inadequate awareness of IGE-AS amongst general neurologists and, arguably, the perennial bias toward diagnosing CPS and temporal lobe epilepsy.

Diagnosis of IGE-AS is possible on clinical grounds when a clear history of a prolonged confusional state is available in a patient with IGE [16]. Such patients may be invited for urgent video-EEG studies when another episode occurs, or undergo video-telemetry, including home video recordings (see Figs. 15.2 and 15.6).

Differential Diagnosis

IGE-AS and IGE-MSE must be differentiated from non-epileptic conditions that include toxic and metabolic states, post-traumatic or transient amnestic states, psychiatric disorders (depression, schizophrenia, or conversion), and migraine aura. As they may also follow a GTCS [16, 51], any prolonged "postictal confusion" should arouse suspicion and prompt EEG recording [59].

Differentiation from focal and other forms of NCSE is extremely important, particularly for patients without a known history of epilepsy at the time of the status, as acute treatment (but also management after the resolution of the episode) is different in IGE. Not infrequently, classification

of the epilepsy type and syndrome diagnosis is achieved by obtaining a full clinical history, an EEG and imaging, and other laboratory studies after the resolution of the status. The main epileptic states that present with clinical and EEG features that may overlap with those of IGE-SE include:

1. ***Temporal Lobe CPSE, Including Transient Epileptic Amnesia (TEA)***

> Rarely, however, the child may be in a state of confusion lasting for hours, which the electroencephalograph proves is a petit mal status. If there is any rigidity of muscles, if the person does automatic purposeless things or if he mumbles, groans or makes chewing motions the attack is probably a short psychomotor seizure and not a petit mal. Involuntary muscle movements, if present, are clonic in petit mal and tonic in psychomotor seizures. Lennox, 1945 [86]

Impairment of consciousness is more frequently mild in IGE-AS, but can range between mild and severe in both conditions. The characteristic for CPSE cycling changes between periods of unresponsiveness and partial responsiveness [57] may be confused with the fluctuations of behavior and mental state that occur in IGE-AS due to varying clustering of discharges and the brief interspersed periods of a normal state.

Clearly "focal" symptoms and signs, such as persistent oro-alimentary automatisms, strongly lateralized motor phenomena (such as dystonic posturing), or dysphasia, suggest CPSE, in which memory is usually severely affected. However, *automatic behavior* and experiential phenomena, such as *déjà vu,* may occur in both forms. On the other hand, regional bilateral (eyelid, perioral, or upper limb) myoclonus would suggest IGE-ASE, although they may appear lateralized, particularly in some inappropriately treated IGE patients [52]. Historical evidence may suggest prior focal seizures, but clinical differentiation between limbic temporal lobe seizures and absences can be exceptionally difficult. Emergency EEG will show focal discharges in the majority of patients with CPSE [65]. In contrast to IGE-AS, in which prompt clinical recovery coincides with normalization of the EEG, clinical response (and recovery of normal cerebral electrical activity) to acute IV treatment is usually gradual and delayed in CPSE, due to the ensuing postictal state [65].

Transient epileptic amnesia (TEA) is a rare but increasingly recognized distinctive *clinical phenotype* of temporal lobe epilepsy. Pure, frequently incomplete, acute amnesia may be the sole ictal symptom [87]; variable retrograde amnesia during the seizure also occurs. Amnesic seizures can last for more than 30 min in about half of patients. A tendency for the attacks to occur on waking may suggest IGE-AS, but in the latter, amnesia is never so selectively (and seldom so severely) affected. Additional ictal symptoms, such as a rising epigastric sensation, *déjà vu* or dysphasia, provide important diagnostic clues when present, but other symptoms like fear and anxiety and myoclonic jerks [87] may also occur in IGE-AS. Interictal, preferably sleep-deprived EEG shows temporal abnormalities.

2. ***Frontal Lobe Nonconvulsive Status Epilepticus (FL-NCSE)***

Convulsive and nonconvulsive frontal lobe status is the commonest extra-temporal focal epileptic state [23–25], and evidence suggests that FL-NCSE may be more frequent than CPSE of temporal lobe onset [28, 88, 89]. FL-NCSE can manifest either as simple focal SE, associated with mild impairment of consciousness and focal symptoms and ictal EEG changes (FL-NCSE type 1), or as complex partial SE, usually with severe impairment of consciousness and bilateral ictal EEG discharges, known as FL-NCSE type 2 [66]. The latter may sometimes mimic IGE-AS from both the clinical and EEG standpoints leading to misdiagnosis, particularly in patients without known epilepsy. Secondary bilateral synchrony (SBS) from strategically positioned foci in the frontal midline is considered as the principal underlying mechanism [90, 91], perhaps in association with a genetic predisposition. However, the reason for which SBS evolves in self-perpetuating thalamocortical oscillations into status is unknown. Employing strict spatial and temporal constraints, Blume and Pillay [92] showed that SBS-GSWD were slower than 3 Hz in 3/4 of the patients, most of whom had frontal lobe foci.

Focal clinical features suggesting FL-NCSE type 2 rather than IGE-AS include lateralized twitching or dystonia, head version, or clear dysphasia, either at seizure onset or during the course of the epileptic state; typically, and at variance with IGE-AS, consciousness is severely affected and there is amnesia for the episode. On the EEG front, in FL-NCSE type 2, bilateral frontally predominant and apparently synchronous discharges frequently follow a lateralized frontal onset; they are usually "slow" at 1–2 Hz [93, 94], and may show "*lateralization*" [66, 93, 95, 96] or be accompanied by "embedded" focal discharges [93]. In addition, FL-NCSE type 2 (as type 1) is usually unresponsive to IV BDZ and VPA, frequently requiring IV PHT or phenobarbital for full seizure control [66, 94].

Notwithstanding the validity of the above diagnostic criteria for most cases of FL-NCSE type 2, electroclinical boundaries with IGE-AS may overlap, making differential diagnosis very difficult—or sometimes, even impossible—at least in the acute phase of the status. Deceptively, episodes of FL-NCSE type 2 can be activated by HV [93, 95, 96], as in IGE, although clear (but frequently forgotten) evidence that focal seizures can also be activated by HV dates to the late 1970s [97]. Incomplete frontally predominant GSWD also occur in IGE, associated with milder loss of

consciousness in both TA [98] and even in prolonged subclinical IGE-AS [99]. In some patients, the frequency of the GSWD in FL-NCSE type 2 is fast, well within the IGE spectrum [91, 95, 96] implying secondary activation and sustained involvement of the thalamocortical system. On the other hand, in later stages of IGE-AS, discharge frequency may drop below 2.5 Hz.

Prolonged emergency video-EEG recordings are necessary to document all aspects of the clinical and EEG evolution of the status, and confident diagnosis may await comprehensive clinical EEG and imaging studies after the resolution of status, particularly in newly presenting patients.

3. **De novo *Absence Status of Late Onset (dnASLO)***

*dn*ASLO is a situation-related prolonged epileptic confusional state that may resemble IGE-AS with regard to clinical presentation and EEG findings but is not considered as part of an epilepsy syndrome or indeed, as a type of epilepsy. *dn*ASLO occurs for the first time in middle-aged or elderly patients without previous history of epilepsy [100].

*dn*ASLO episodes are usually triggered by acute withdrawal of chronic psychotropic medication, mainly BDZs [100, 101], but also tricyclic antidepressants. They can also occur during electroconvulsive therapy, angiography, and metrizamide myelography, in acute or chronic alcoholism, and in toxic or metabolically abnormal states [102]. Patients often have a history of psychiatric illness treated with multiple psychotropic drugs.

Differentiation from IGE-AS is clinically important because management and prognosis are different. Patients with IGE-AS are at risk of further generalized seizures, so they need syndrome diagnosis and maintenance treatment with appropriate ASDs. For those with *dn*ASLO, identification and removal of the offending factor may suffice. The overall prognosis is excellent, with little risk for recurrence [100]. Differentiation is not always easy or immediately possible, particularly in elderly patients. In the emergency ictal EEG, the frequency of GSWD in *dn*ASLO is usually slower than 2.5 Hz [102, 103], but slower frequencies and irregular patterns also occur in IGE-AS. Also, both IGE-AS and *dn*ASLO typically respond to IV injection of BZDs, with resolution of ictal EEG activity, emergence of normal background rhythms, and clear clinical improvement (Fig. 15.7). From the clinical viewpoint, middle-aged and elderly individuals *with* a past history of IGE can present with IGE-AS episodes, sometimes under circumstances that may appear similar to those which can trigger *dn*ASLO, including alcohol consumption (but not intoxication or withdrawal [5]) or sudden ASD changes (e.g., discontinuation of BDZ) as part of their ongoing treatment [11], or simply as a late complication [10, 104, 105]. Furthermore, IGE-AS in middle-late adult life may be the first *overt* clinical manifestation of IGE, although clinical and EEG followup after the episode may show evidence of earlier IGE [5, 106]. Therefore, a late onset of AS per se should not necessarily be taken as unequivocally diagnostic of *dn*ASLO. In the acute presentation, both possibilities should be evaluated, and clinical and video-EEG follow up *after* the resolution of the status are mandatory to guide further management and treatment.

*dn*ASLO is a type of *acute symptomatic seizure* that may not recur if the triggering factors can be identified and corrected. Therefore, long-term treatment with ASDs may not be needed [100]. Diagnosis requires: (1) emergency EEG with IVBZD to confirm the epileptic nature of the episode (similarly slow, <2 Hz, repetitive generalized epileptiform patterns in hypoxic and drug-induced encephalopathies may partly or completely resolve, but the emerging background rhythms will be abnormal and there will be no clinical improvement [59]); (2) unequivocal evidence of an exogenous trigger or precipitant, mainly psychotropic drug withdrawal or acute metabolic or toxic insults; (3) no evidence of IGE by virtue of history *and* prospective electroclinical evaluation.

Cryptogenic Generalized Epilepsies

1. ***Epilepsy with Myoclonic–Astatic Seizures (MAE) and Lennox–Gastaut Syndrome (LGS)***

MAE is genetically determined, non-lesional, age-dependent generalized epilepsy that affects previously normal children between the ages of two and five years of age. It has a variable course, ranging from (eventually) good responsiveness to treatment with normal cognitive function, to nonprogressive epileptic encephalopathy with intractable seizures and cognitive impairment. Therefore, it may clinically overlap with IGE. The interictal EEG shows GSWD at 2–3 Hz increasing during sleep, and the background remains normal in children with mild forms.

Episodes of IGE-AS/IGE-MSE occur mostly spontaneously in a fourth to a third of children, mainly in those with unfavorable outcome, and last from hours to several weeks. They are characterized by depressed consciousness and responsiveness, multifocal arrhythmic twitching in the limbs and face, and diffuse spike-wave discharges on the EEG (Fig. 15.8). MAE shares many clinical features with cryptogenic LGS, particularly in its myoclonic form, in which frequent episodes of myoclonic status occur, associated with behavioral depression and erratic myoclonus [107].

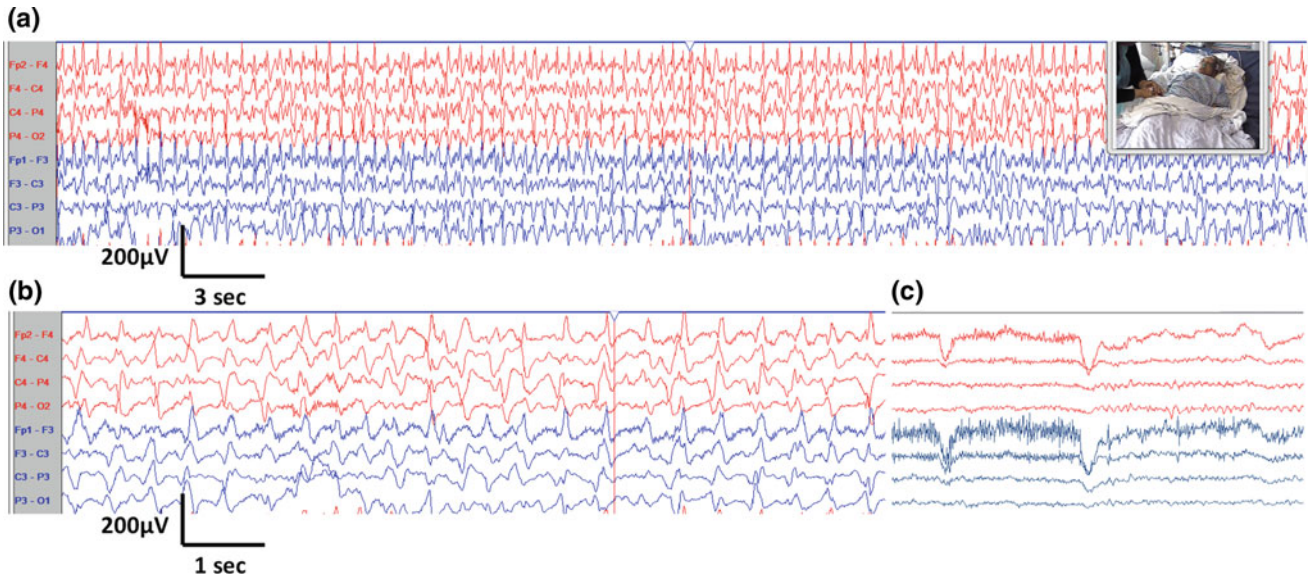

Fig. 15.7 *De novo* absence status of late onset in a 72-year-old woman after benzodiazepine withdrawal. **a** Ongoing generalized spike-wave discharges of anterior predominance; the patient is confused and unresponsive. **b** At conventional "paper speed," discharges are bilateral and synchronous at around 2 Hz but show triphasic configuration rather than the typical spike-wave appearance of the idiopathic AS. **c** 1 mg of IV clonazepam resulted in complete electroencephalogram (*EEG*) normalization and clear clinical improvement. She had no prior history of epileptic seizures, including prolonged states of confusion. She developed no further seizure symptoms within 18 months of follow up, and a sleep-deprived EEG six months after this recording was normal

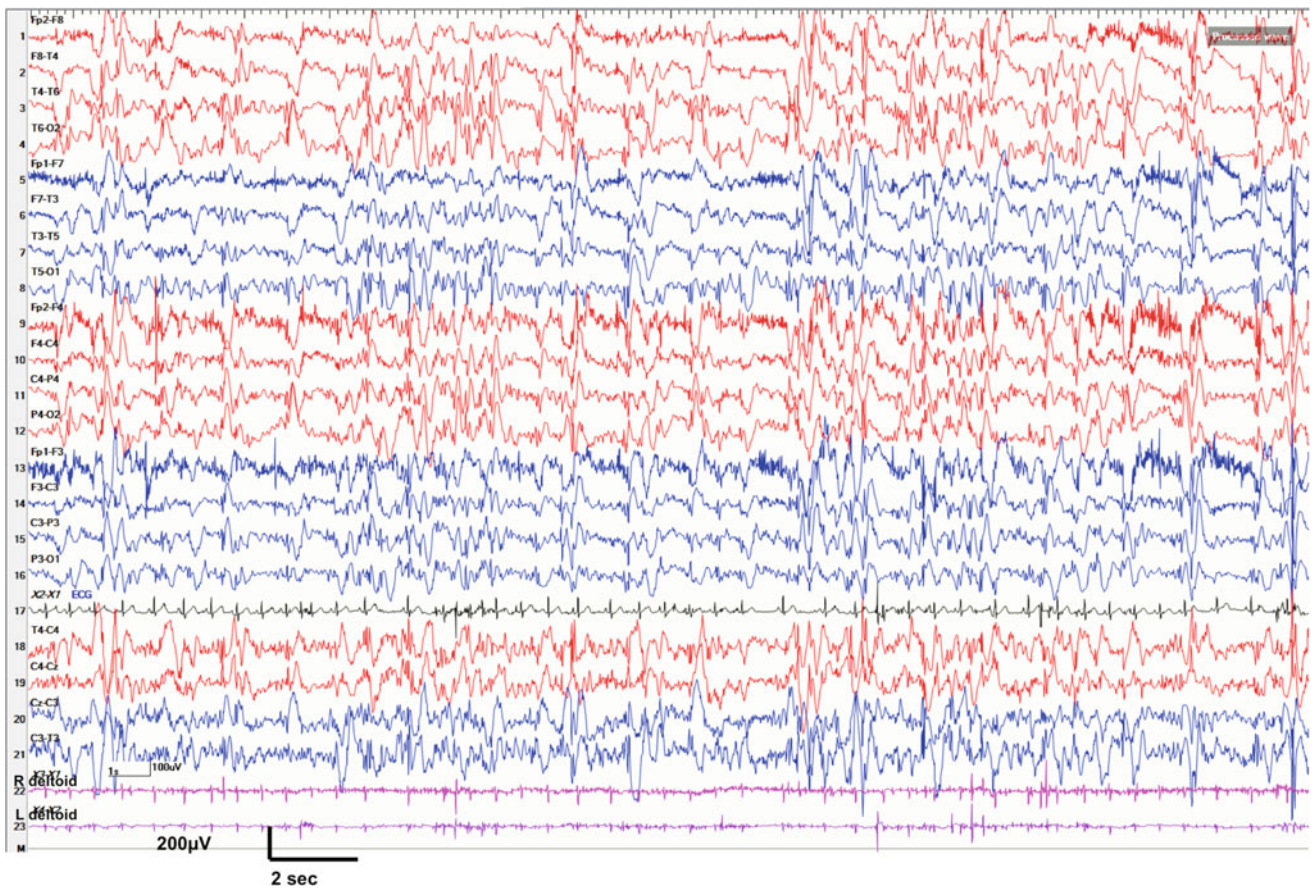

Fig. 15.8 Myoclonic status in an 8-year-old girl with epilepsy with myoclonic-astatic seizures. Diffuse and irregular spike and polyspike-and-wave discharges, with erratic myoclonus recorded on the electromyogram channels

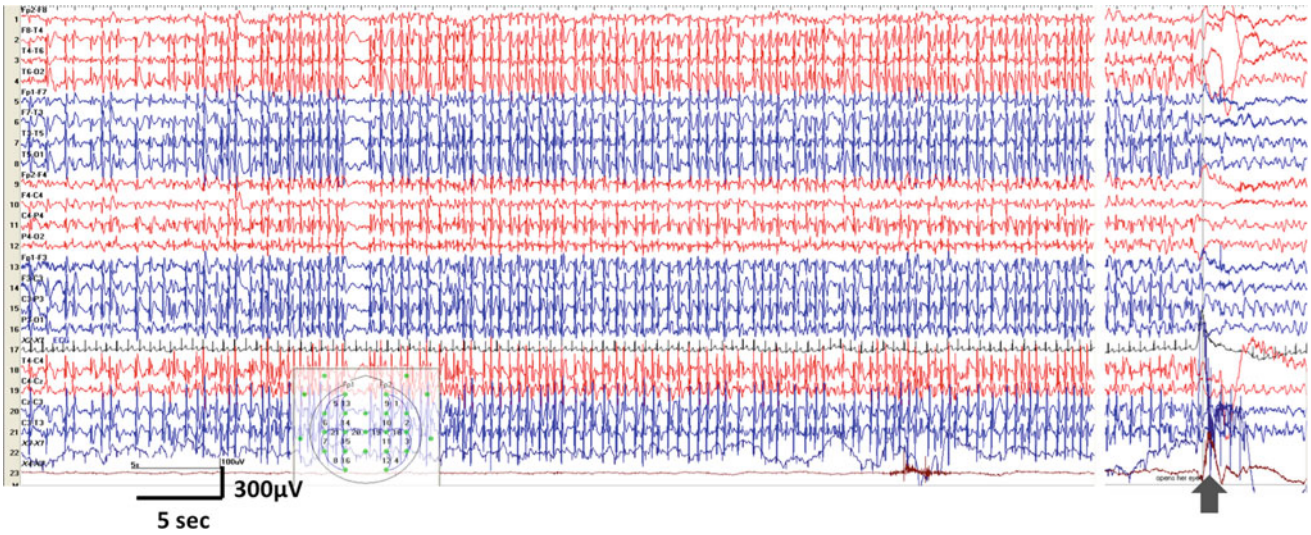

Fig. 15.9 ESES syndrome in a girl with daytime typical and atypical absences, with eyelid flickering and language and global regression. Magnetic resonance imaging was normal. The continuous pattern ceases abruptly as she wakes up (*arrow on the right*)

2. ***Encephalopathy with Status Epilepticus During Sleep or ESES (Including Acquired Epileptic Aphasia or Landau–Kleffner Syndrome)*** [108]

There has been significant confusion about this syndrome on both sides of the Atlantic [109]. ESES is characterized by (1) neurological (cognitive, motor, and behavioral) deterioration; (2) various seizure types; and (3) a distinctive EEG pattern characterized by continuous spike-wave activity during slow sleep, a *frank nonconvulsive epileptic state*.

Generalized spike wave during slow sleep is *responsible* for the cognitive impairment. It consists of continuous or sub-continuous bilateral and diffuse slow spike-and-waves, mainly at 1.5–2.5 Hz, appearing as soon as affected children fall asleep and persisting through all non-REM sleep stages. Typically, the spike-wave index (the percentage of slow sleep occupied by epileptic activity) is >85%, although lower thresholds can also be diagnostic in the right clinical context. Topography may appear diffuse in non-symptomatic cases (Fig. 15.9). Diagnosis requires EEG recording during sleep, but also during a period of wakefulness before sleep onset and after awakening.

3. ***Ring Chromosome 20 Syndrome (r20S)*** [110]

NCSE in r20S is probably best described as a mainly absence status with an associated myoclonic component. Episodes take the form of prolonged confusional and variably amnesic or twilight states, with facial or limb myoclonus, ambulatory or persevering automatisms, or even complete arrest and muteness, and may recur several times in the same day. Ictal EEG commonly shows diffuse high voltage rhythmic 2–4 Hz slow waves with variably intermixed frontally predominant spike-wave activity. Middle-aged patients may be misdiagnosed with *dn*ASLO if previous episodes are not identified, and frontal lobe status should be also considered in view of the affective and autonomic symptoms and the anterior predominance of the EEG abnormalities. Dysmorphisms are subtle or may not exist, delaying the diagnosis.

Absence status has been reported in 17% of children with epilepsy with myoclonic absences [111], but myoclonic absence status is rare. Other pediatric epileptic syndromes that are associated with atypical absence or myoclonic status epilepticus, including severe myoclonic epilepsy in infancy, Angelman syndrome, nonconvulsive epileptic states in idiopathic focal epilepsies of childhood, and nonprogressive symptomatic encephalopathies, are outside the scope of this chapter and are presented in Chap. 27, "Pediatric Status Epilepticus: Initial Management and the Special Syndromes of Status Epilepticus in Children."

Treatment and Outcome

GCSE-IGE is never the initial presentation of the disease, and in patients with known IGE it typically occurs as a result of poor compliance, taking the form of repetitive GTCS and responding to IVBZD, rather than that of uninterrupted established convulsive status [112]; IVVPA may be preferable as it can increase possibly sub-therapeutic blood levels or ease the transition to appropriate maintenance treatment, when needed.

The treatment of IGE-AS and IGE-MSE is described in Chap. 22, "Initial Treatment of Nonconvulsive Status Epilepticus." As there is no clinical evidence of ensuing morbidity [16, 113], aggressive treatment is rarely needed [114].

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Early Treatment of Convulsive Status Epilepticus

16

Abeer J. Hani and Aatif M. Husain

Introduction

Convulsive status epilepticus (CSE) is a neurologic emergency that requires early identification and intervention given its association with significant morbidity and mortality. The incidence of status epilepticus (SE) in the general population is estimated at 60 per 100,000 per year [1]. The overall mortality is about 20% [2].

The definition of CSE is continuous convulsive seizure activity lasting for more than 5 min, or 2 or more seizures without recovery of consciousness in between [3]. The duration criterion for SE has long been the subject of debate. Most recently, the International League Against Epilepsy (ILAE) redefined SE as ongoing seizure activity due to failure of mechanisms responsible for seizure termination, or initiation of mechanisms provoking ongoing seizures, causing prolonged seizures after time point *t*1, and which can have long-term consequences after time point *t*2. Values for t1 and t2 are 5 min and 30 min, respectively, for CSE [4]. The *t*1 for other types of SE is also 5 min, but *t*2 is not known.

The importance of timely management of SE stems from the dire consequences that prolonged seizures may have in both animals and humans. SE may result in neuronal loss, reactive gliosis, and aberrant synaptic reorganization of surviving cells, with the effect more significant the longer the seizure lasts [5].

A.J. Hani
Department of Pediatrics and Neurology, Gilbert and Rose-Marie Chagoury School of Medicine, Lebanese American University, P.O. Box 13-5053Chouran, Beirut, Lebanon
e-mail: abeer.hani@lau.edu.lb

A.M. Husain (✉)
Department of Neurology, Duke University Medical Center, Box 102350, 299B Hanes House, 315 Trent Drive, Duke University Medical Center, Durham, NC 27710, USA
e-mail: Aatif.husain@duke.edu

A.M. Husain
Neurodiagnostic Center, Veterans Affairs Medical Center, Durham, NC 27705, USA

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Depending on how long SE lasts and how it responds to treatment, four stages of SE have been suggested: early, established, refractory, and super-refractory [6]. Early SE consists of SE that responds to first-line treatment with benzodiazepines (BZDs), whereas established SE refers to SE that persists after treatment with first-line therapy. Refractory SE occurs when SE fails to stop after first and second-line anti-seizure drugs (ASDs) have been given. Super-refractory SE is defined as SE that continues or recurs 24 h or more after the onset of 'anesthetic' treatment. This chapter covers the treatment of early and established CSE.

General Principles of Management

Initial management of CSE consists of (1) life support measures, (2) rapid initiation of treatment, and (3) simultaneous evaluation of the underlying etiology [7]. The aim of rapid intervention is to terminate the SE, prevent its recurrence, and manage any complications.

Life Support Measures

In managing patients with CSE, close monitoring of vital signs is recommended. Often, oxygen supplementation is warranted. Airway, breathing, and circulation need to be surveyed systematically, and ventilator support may be required as the seizure progresses and fails to respond to first or second-line therapy.

Evaluation

In determining the etiology of the CSE, pertinent history (including history of epilepsy if applicable), recent change or noncompliance of ASDs, recent infections, alcohol or illicit substance use, previous brain injury, relevant family history, and recent illnesses need to be investigated. Initial laboratory

studies include glucose, serum chemistries, arterial blood gas, ASD levels (if applicable), complete blood count, and urine and serum toxicology. A lumbar puncture may be indicated to evaluate for central nervous system (CNS) infections, if suggested by the history, and brain imaging may be indicated. Recently, the identification of autoimmune encephalitis as a cause of SE warrants evaluation, when suggested by the history. In addition to this workup, electroencephalography (EEG) monitoring is recommended to evaluate for ongoing nonconvulsive status epilepticus (NCSE) or nonconvulsive seizures, especially in patients with ongoing altered mental status or those who are sedated.

Treatment of Convulsive Status Epilepticus

The mainstay of treatment of CSE is pharmacologic. The choice of medications, and which BZD, has been the subject of debate and will be detailed below.

Prognostic predictors in SE have been well defined and include age at onset, underlying etiology, SE severity, and medical comorbidities [7].

Rapid initiation of treatment and intervention is considered the most important predictor of outcome. This has led to a recommendation that in-house protocols for the general management of SE are important to streamline management and avoid delays in treatment. Ideal treatment for SE would stop all seizure activity immediately, be administered easily and rapidly, and have minimal if any adverse effects [8].

Pharmacologic Therapy

To provide guidance for the acute management of SE, the European Federation of Neurological Societies, the Neurocritical Care Society, and the American Epilepsy Society have each issued practice guidelines (Fig. 16.1) [9–11].

Table 16.1 includes a summary of the recommendations of each of these Societies. Here, first and second-line therapies will be detailed. Table 16.2 shows a list of dosing recommendations and common side effects of some first and second-line therapies for SE [12].

First-Line Therapy

The value of BZDs as first-line treatment for SE has been confirmed in multiple prospective trials. BZDs may be administered by parenteral routes (rectal, intranasal, buccal, or intramuscular [IM] formulations) when used in-house or in out-of-hospital settings, or if possible, orally. To date, rectal diazepam (DZP) is the only marketed treatment available for use by nonmedical caregivers in the United States, and buccal midazolam (MDZ) is approved for use in the European Union [13]. Various BZDs and their modes of administration are discussed below.

The most common adverse effects of BZDs are respiratory depression and systemic hypotension, and both are dose-related. A less common adverse effect is cardiac arrhythmia. The rate of adverse effects ranges between 12 and 53% in a few studies of generalized CSE [14–16].

Rectal Diazepam. Rectal DZP is an appealing choice for the out-of-hospital or in-house settings where parenteral access is hard to establish. It is used more in the pediatric population.

DZP is highly lipid soluble and is rapidly absorbed by the mucosa, with good penetrance of the CNS. Peak plasma levels following rectal administration are reached in 10 to 60 min, with a bioavailability of 80–98% [17, 18].

Multiple studies have investigated the efficacy of rectal DZP in the treatment of acute repetitive seizures. The North American Diastat Study Group found that 55% of patients who received rectal DZP became seizure-free, compared to 34% given placebo ($p = 0.03$) [19]. Another study noted seizure termination in 64% of patients who received rectal DZP, compared to 24% of those given placebo ($p < 0.0001$) [20]. Both studies showed that rectal DZP was safe, with no significant difference in the rates of adverse events between the two groups, and with drowsiness the most common adverse event.

Buccal Midazolam. Buccal MDZ is another BZD formulation that may be used in out-of-hospital settings—with a practical advantage. It consists of liquid MDZ applied over the gums, which are highly vascularized, allowing for rapid absorption and avoidance of first-pass metabolism [21]. A few studies have compared the efficacy of buccal MDZ to rectal DZP. One found no significant difference in seizure cessation within 10 min between buccal MDZ (75%) and rectal DZP (59%) ($p = 0.16$) in institutionalized children with severe symptomatic epilepsy [22]. In another study of 177 children presenting to the emergency room with acute seizures, buccal MDZ was more effective than rectal DZP (56% vs. 27%), with similar rates of adverse events [23]. This mode of administration was easier to administer and more acceptable socially than the rectal formulation. Buccal MDZ was compared to intravenous (i.v) DZP in children in one study, with no difference in overall efficacy (defined as complete cessation of seizures 5 min after administration of the study drug) [24].

Intranasal Midazolam. Intranasal MDZ makes use of the large surface area of the mucus membranes of the nasopharynx, allowing for rapid absorption and avoidance of first-pass metabolism [25]. Peak plasma concentrations were achieved about 14 min after administration, with a bioavailability reaching 85%. A prospective randomized trial in children with febrile seizures compared the efficacy of intranasal MDZ to that of IVDZP in the emergency room

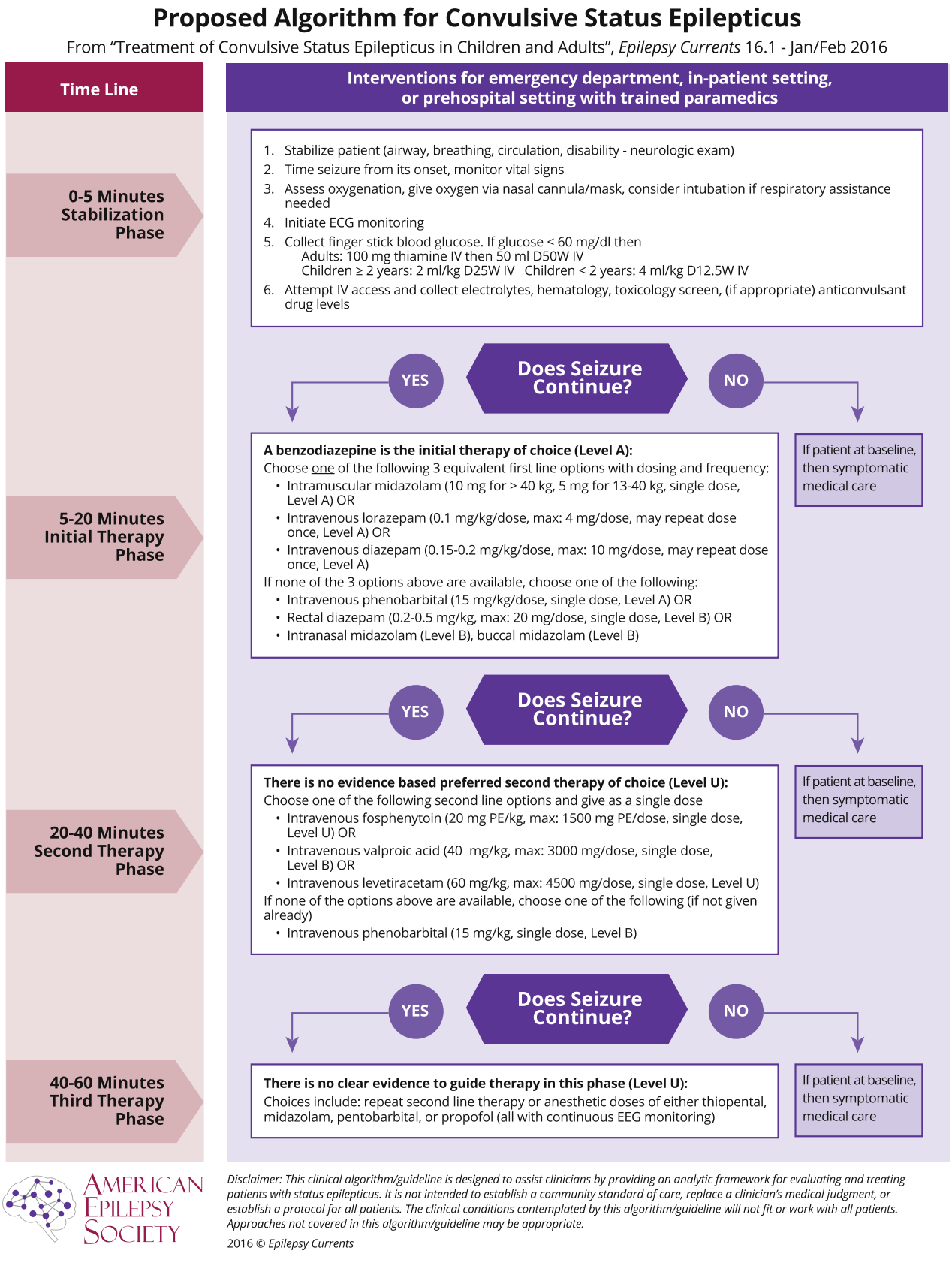

Fig. 16.1 Proposed algorithm for the treatment of status epilepticus (From Glauser et al. [11], with permission). Image courtesy of the American Epilepsy Society

Table 16.1 Summary of Recommendations of available guidelines for management of status epilepticus (Modified from Unterberger [7], and Glauser et al. [11])

	EFNS guidelines, 2010 [9]	NCS guidelines, 2012 [10]	AES guidelines, 2016 [11]
Definition of Status Epilepticus	Operational definition: seizure duration > 5 min	Seizure duration > 5 min	Seizure duration more > 5 min
General management	– Appropriate neurocritical care management – Identify cause urgently, and treat if possible	– Appropriate neurocritical care management – Identify cause urgently, and treat if possible – Head CT – C-EEG monitoring	– Appropriate neurocritical care management – Identify cause urgently, and treat if possible
Initial pharmacologic treatment for GCSE (level A evidence)	Level A evidence: – IV lorazepam – IV diazepam + phenytoin or fosphenytoin – Prehospital treatment recommended with IV lorazepam or diazepam	– Level A evidence: BZDs given as emergency initial therapy (IV lorazepam, IM midazolam, rectal diazepam) – Followed by IV ASD for urgent control (Phenytoin, phenobarbital, valproic acid, levetiracetam, continuous midazolam)	Level A evidence: – IV lorazepam – IV diazepam – IM midazolam If above three not available, IV phenobarbital

EFNS European Federation of Neurological Societies, *NCS* neurocritical care society, *AES* American Epilepsy Society, *CT* computed tomography, *C-EEG* continuous electroencephalography, *BZDs* benzodiazepines, *IV* intravenous, *IM*-intramuscular, *GCSE* general convulsive status epilepticus, *ASD* anti-seizure drug

Table 16.2 Dosing recommendations and adverse effects of first and second-line therapy for convulsive status epilepticus, 2016 (Adapted and modified from Smith et al. [12], with permission)

Medication	Recommended dosing	Serious adverse effects
Lorazepam	IV: 0.1 mg/kg IV, up to 4 mg per dose; may repeat in 5–10 min	Hypotension, respiratory depression
Diazepam	IV: 0.15–0.2 mg/kg IV, up to 10 mg per dose; may repeat in 5 min Rectal: 0.2–0.5 mg/kg, up to 20 mg	Hypotension, respiratory depression
Midazolam	Adult IM: 0.2 mg/kg, up to 10 mg Ped IM: 5 mg if 13–40 kg, 10 mg if > 40 kg, 0.3 mg/kg, up to 10 mg Intranasal: 0.2 mg/kg Buccal: 0.5 mg/kg	Hypotension, respiratory depression
Phenytoin *or* Fosphenytoin	20 mg/kg IV; may give additional 5–10 mg/kg 20 mg PE/kg IV; may give additional 5–10 PE/kg	Hypotension, arrhythmias, purple glove syndrome (phenytoin)
Levetiracetam	20–60 mg/kg IV	Aggression
Phenobarbital	15–20 mg/kg IV; may give an additional 5–10 mg/kg	Hypotension, respiratory depression
Valproic acid	20–40 mg/kg IV, may give an additional 20 mg/kg	Hyperammonemia, pancreatitis, thrombocytopenia, hepatotoxicity
Lacosamide	Pediatric IV: 8–10 mg/kg Adult IV: 200–400 mg	Cardiac arrhythmia, PR interval prolongation, dizziness, ataxia, nausea, diplopia

IV intravenous, *IM*-intramuscular, *PE* phenytoin equivalent, *PR* PR interval in electrocardiography, or time from the onset of the P wave to the start of the QRS complex

[26]. The two treatments had equal efficacy controlling seizures (88% with MDZ; 92% with DZP), with no significant adverse effects in either group. Time to administration of intranasal MDZ was faster, but the time period between drug administration and seizure cessation was shorter for the IVDZP group. Another trial compared use of intranasal MDZ to rectal DZP in 92 children for prehospital seizures lasting more than 5 min [27]. There was no difference in the total seizure time after medication administration of the two therapies.

Intranasal Lorazepam. Intranasal lorazepam (LZP) is similar to intranasal MDZ, with peak plasma concentrations

achieved in 30 min and a bioavailability of about 80% [28]. A study of children with ongoing seizures in the emergency room compared IVLZP to intranasal LZP, both at a dose of 0.1 mg/kg, with a maximum dose of 4 mg [29]. There was no difference detected between the two formulations of LZP based on clinical seizure remission within 10 min of administration of the study drug, establishing the non-inferiority of intranasal LZP compared to IVLZP.

Sublingual Lorazepam. Sublingual LZP was compared to rectal DZP in a randomized controlled trial conducted across nine hospitals in Sub-Saharan Africa involving 436 children [30]. The efficacy of sublingual LZP (56%) was significantly lower than that for rectal DZP (79%) for terminating seizures within 10 min of study drug administration.

Intramuscular Midazolam. MDZ has a benzene ring that opens at an acidic pH, making it water soluble, such that it is absorbed promptly at injection sites. Once in the blood stream, the benzene ring closes upon exposure to the slightly basic physiologic pH, and MDZ becomes lipid soluble [31]. When injected IM, peak plasma concentration is achieved within 23–40 min, with a bioavailability of about 87% [32, 33]. DZP and LZP are lipid soluble and tend to be absorbed slowly and irregularly after IM injection.

A multicenter double-blind randomized non-inferiority trial (the RAMPART, Rapid Anticonvulsant Medication Prior to Arrival Trial) compared IMMDZ to IVLZP in adults and children with SE [34]. The primary outcome [of seizure cessation without need for additional rescue therapy at the time of arrival in the emergency department] was achieved in 73% of subjects in the IMMDZ group compared with 63% of subjects in the IVLZP group, demonstrating the non-inferiority of IMMDZ. Other studies have compared IMMDZ to IVDZP, with a shorter interval to seizure cessation found with IMMDZ but similar overall efficacy for seizure termination [35].

Intravenous Lorazepam and Diazepam. IVLZP is fast acting, with a median latency of about 3–11 min and a long duration of action (12–24 h) [16, 36, 37]. IVDZP has a median onset of action between 2 and 15 min, with rapid entry into the CNS but has a short duration of action, with a drop of the level by about two-thirds in the first 2 h after administration given its large volume of distribution [16, 38, 39]. IVLZP and DZP are the recommended in hospital first-line therapies for CSE in the various practice guidelines.

Out-of-hospital use of IVDZP and LZP has also been investigated. The San Francisco trial of IVBZD administered by paramedics was a randomized, double-blinded, placebo-controlled trial with 3 arms: IVLZP, IVDZP, or placebo, administered to 205 adults with generalized tonic–clonic seizures lasting more than 5 min [15]. IVLZP was effective in terminating seizures by arrival in the emergency department in 59% of cases, compared with 42.6% with IVDZP, and 21% with placebo. There was no statistically significant difference between IVLZP and IVDZP in efficacy, but both were superior to placebo in efficacy and with respect to cardiorespiratory complications.

The Veterans Affairs Status Epilepticus Cooperative Study included 384 patients in overt generalized CSE who were randomized to one of four IV treatment arms: LZP, phenobarbital (PB), DZP plus phenytoin (PHT), or PHT alone [14]. The primary outcome of this study was cessation of all motor and electrographic seizure activity within 20 min of starting the drug infusion, with no recurrence of seizure activity over the next 40 min. LZP stopped the seizure activity in 65% of cases, phenobarbital in 58%, the DZP and PHT combination in 56%, and PHT alone in 44%. Pairwise comparisons between the different arms showed that LZP was superior to the other treatment arms and was easier to administer, hence the study recommended LZP as the best initial therapy for generalized CSE.

Second-Line Therapy

Second-line therapy is used when SE has failed to respond to BZDs. For IV administration, this therapy may include PHT, fosphenytoin (FOS), PB, valproic acid (VPA), levetiracetam (LEV), or lacosamide (LCM).

Phenytoin and Fosphenytoin. Phenytoin has long been used in the treatment of SE. The pharmacokinetic profile includes peaking of brain concentrations within 10 min of IV administration and onset of the anticonvulsant effect within 3 min [40, 41].

Fosphenytoin is a PHT prodrug, metabolized following infusion into the active drug PHT [42]; it may be administered IV or IM. FOS has equal effectiveness to PHT and may be administered by a peripheral IV line, given that it causes less local irritation at the infusion site and is less likely to cause tissue necrosis than does PHT if extravasated [43]. The adverse effects associated with FOS include ataxia, dizziness, nystagmus, somnolence, and hypotension and arrhythmia with rapid infusions, all of which are also attributable to PHT—with the exception of paresthesia of the groin, buttocks, or face, seen more with FOS. The recommended loading dose of PHT is usually 20 mg/kg and that of FOS 20 mg "phenytoin equivalent" (PE) per kg. If SE persists after this loading dose, an additional 5–10 mg/kg may be given and the PHT levels monitored.

In several studies of SE and acute repetitive seizures, IVPHT has terminated seizures in about 40–90% of cases [44–46].

Valproic Acid. Valproic acid (VPA) is water soluble, allowing for its administration at a more physiologic pH along with other medications. It can be delivered rapidly with boluses of 20–30 mg/kg/dose infused in under 10 min,

with no significant side effects [47, 48]. It causes minimal sedation, respiratory depression, or hypotension.

There have been several studies comparing the use of IVVPA to that of other ASDs as first-line therapy for SE. In one study, VPA was statistically more effective in aborting seizures in patients with CSE than was PHT (66% vs. 42%) [49], but it was similar to PHT (87.8% vs. 88%) in another [50]. In adults with SE that failed to respond to initial BZD therapy, the efficacy of VPA was similar to that of PHT (88% vs. 84%) in one study [51] and similar to that of continuous DZP infusion (56% vs. 50%) in another [52].

Phenobarbital. Phenobarbital has been used intravenously for many years to treat SE and continues to be used commonly in neonates and children. The loading dose is 15–20 mg/kg. One study evaluated the efficacy of phenobarbital vs a combination of PHT and DZP in stopping generalized CSE [38]. PB was slightly more efficacious than the combination therapy in cumulative convulsion time and in response latency. Subsequent trials favored the use of BZDs over PHT and suggested deferral of PB use for more refractory cases of SE [53].

Levetiracetam. Levetiracetam has an appealing side effect profile, and its IV use in the treatment of SE has been investigated in a few trials. In a randomized controlled trial in children with CSE, IVLEV at 20 mg/kg/dose was effective in 75.6% of cases, compared to 76.3% using IVLZP (0.1 mg/kg/dose) [54]. Several retrospective trials have also demonstrated efficacy of IVLEV when used as first-line therapy to treat CSE [55–58].

Lacosamide. Current evidence on the use of IV lacosamide is mostly restricted to retrospective studies [59, 60], with a recommended bolus of 200–400 mg (or possibly higher] given IV. There has been more interest in researching the use of IV LCM in refractory SE [61].

Conclusion

CSE is a neurologic emergency requiring prompt diagnosis and management. Out-of-hospital as well as in-house identification and treatment using various formulations (IM, IV, buccal, intranasal, and rectal) of several BZDs is now considered first-line therapy. Subsequently, in case of persistence of the seizure activity, second-line therapy including IVPHT, phenobarbital, and VPA may be used. Recently, there has been growing interest in investigating newer ASDs with IV formulations that have a more favorable side-effect profile. The aim of management is rapid cessation of seizure activity, and this is best done using a well-structured in-house protocol known well to all medical personnel so as to streamline the evaluation and treatment of all patients presenting with convulsive status.

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Treatment of Refractory and Super-Refractory Status Epilepticus

17

Sara Hocker

Introduction

Refractory and super-refractory status epilepticus (SE) are acute neurologic emergencies with mortality rates of 18–26% [1–4] and 23–48% [5–10], respectively. Over half of survivors have poor functional outcomes [10–12], but excellent outcomes are reported even after prolonged SE lasting weeks or months [13, 14]. The pharmacologic treatment itself portends additional risk of morbidity and mortality, and recent evidence highlights these concerns [15–17]. Although there are risks of treatment, uncontrolled convulsive SE may be fatal or lead to permanent multi-organ failure [18, 19]; therefore, aggressive control of seizures is critical. When nonconvulsive SE, whether focal or generalized, leads to a reduction in the level of consciousness and significant compromise of function, seizures must also be controlled aggressively, despite the inherent treatment risks. Predictors of refractoriness include severity of consciousness impairment at onset, de novo episodes, and encephalitis [7, 9], but SE of any cause can become refractory if initial therapies are delayed or inadequate, or if the underlying cause is not reversed.

If SE is refractory to initial therapies including benzodiazepines and a second line intravenous (IV) anti-seizure drug (ASD) such as fosphenytoin, valproic acid, or phenobarbital, the patient is said to be in refractory status epilepticus (RSE) and treatment with an anesthetic drug is frequently initiated. When SE continues or recurs 24 h or more after the initiation of anesthetic treatment, it is termed super-refractory status epilepticus (SRSE), or alternatively, 'malignant status epilepticus.' The pharmacologic treatment of this very refractory group of patients is not well determined or supported by strong evidence [20, 21].

S. Hocker (✉)
Division of Critical Care Neurology, Department of Neurology, Mayo Clinic, 200 First Street SW, Rochester, MN 55905, USA
e-mail: hocker.sara@mayo.edu

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This chapter provides a comprehensive overview of the pharmacologic treatment of refractory and super-refractory status epilepticus. Treatment aggressiveness, drug selection, and dosing are discussed, including both anesthetic and non-anesthetic ASDs. An in depth review of commonly used anesthetic drugs including propofol, midazolam, ketamine, and barbiturates including thiopental, phenobarbital, and pentobarbital, is provided. Mirroring the daily care of patients with refractory and super-refractory status epilepticus, the chapter emphasizes the complications of anesthetic therapies and when possible, how to prevent them. Less frequently discussed aspects of treatment, including the electroencephalography (EEG) suppression target, principles of weaning anesthetic drugs, and what to do in between weaning attempts, are addressed. Also included is a section on when and how to initiate a trial of immunotherapy for cryptogenic or antibody-mediated RSE.

Refractory Status Epilepticus

Selection of Third Line Therapy

After failure of an adequate dose of first line (i.e., a benzodiazepine) and a second line ASD (e.g., fosphenytoin), SE is considered refractory. The main decision point at this stage is whether to treat with a third line non-anesthetic ASD or to initiate a continuous anesthetic infusion. Numerous options and little data exist to guide this decision. The only randomized controlled trial designed to evaluate this phase of SE was stopped prematurely due to poor enrollment [22]. Continuous infusion IV anesthetic drugs are often employed to control RSE, especially in convulsive SE. Purported reasons for this aggressive approach include; (1) prevention of systemic injury or death from uncontrolled convulsive SE, (2) prevention of seizure-induced neuronal loss, (3) reduction of cerebral metabolism, and (4) the assumption of lower efficacy of third or fourth line non-anesthetic ASDs. Undoubtedly, uncontrolled convulsive seizures cause

neuronal injury and may lead to severe and permanent systemic and neurologic morbidity [19, 23]. Neuronal injury may well also occur with uncontrolled nonconvulsive seizures [24–26], and the decline in neurologic function appears to be directly proportional to the duration of nonconvulsive seizures [27]. Nevertheless, the use of anesthetic drugs in the doses required to control RSE is associated with serious side effects, some of which can also result in death [19].

Given the limited evidence supporting the use of anesthetic drugs and the relatively unfavorable side effect profiles, multiple recent retrospective observational studies were performed to assess the association between anesthetic drug use and outcome in RSE [15–17], the results suggesting an independent association with mortality and worse functional outcomes. The first of these studies did not adequately control for known outcome predictors [15]. Sutter and colleagues then reviewed 171 consecutive patients with non-anoxic SE of whom 63 (37%) were treated with an anesthetic drug [16]. They controlled for known outcome predictors including duration of SE, critical comorbid medical conditions, SE severity (graded by the Status Epilepticus Severity Score [STESS]), and administration of non-anesthetic third line ASDs. The STESS includes patient age, worst seizure type, level of consciousness at presentation, and whether or not the patient has a history of seizures [28]. The authors found that the use of an anesthetic drug was associated with increased mortality (relative risk 2.88) and worse functional outcomes (relative risk 1.25), but the difference in outcomes was most pronounced in those with focal seizure types, as opposed to convulsive or nonconvulsive SE in coma [16]. The patients who received anesthetic drugs were more likely to have a depressed level of consciousness prior to treatment, an acute symptomatic etiology, and a longer duration of SE. After adjusting for refractoriness, the association of anesthetic drug use with mortality and functional outcome disappeared [16]. Marchi et al. [17] reviewed 467 consecutive episodes of SE lasting longer than 30 min, among whom 50 (10.7%), were managed with an anesthetic drug. After adjusting for etiology, severity of SE (using the SESS), and comorbid conditions, the use of an anesthetic drug was associated with new disability at hospital discharge (relative risk of 4.6) and mortality (relative risk 5.5). Similar to the results of Sutter and colleagues, the effect was most pronounced for those with milder seizure types, and patients treated with anesthetic drugs were more likely to have severe seizure types (convulsive or nonconvulsive SE in coma) [17].

What is clear from these studies is that patients who require anesthetic drugs for control of RSE have more severe and refractory forms of SE, and that in this patient subgroup of patients outcomes are often poor. It remains unknown how much brain function is being saved in survivors by aggressively controlling the seizures and whether this justifies the risks of anesthetic drug use. In fact, one paper showed that a higher dose anesthetic drug infusion was superior to a lower dose of the same drug (midazolam), resulting in fewer withdrawal seizures and lower mortality [29].

Incorporating the lessons of these studies, Fig. 17.1 depicts a simple algorithmic approach to selection of third line therapy in RSE. As a general principle, refractory generalized convulsive SE should be controlled as rapidly as possible with the use of an anesthetic drug, and control confirmed by continuous electroencephalogram (C-EEG). The decision to initiate an anesthetic drug necessitates admission to an intensive care unit (ICU), endotracheal intubation and mechanical ventilation, continuous hemodynamic monitoring, and initiation of C-EEG monitoring. Nonconvulsive RSE presents less risk to the cardiopulmonary, musculoskeletal and renal systems, and possibly the brain. Thus, in patients who are hemodynamically stable, have preserved airway reflexes and are adequately oxygenating and ventilating, it is reasonable to try one or two

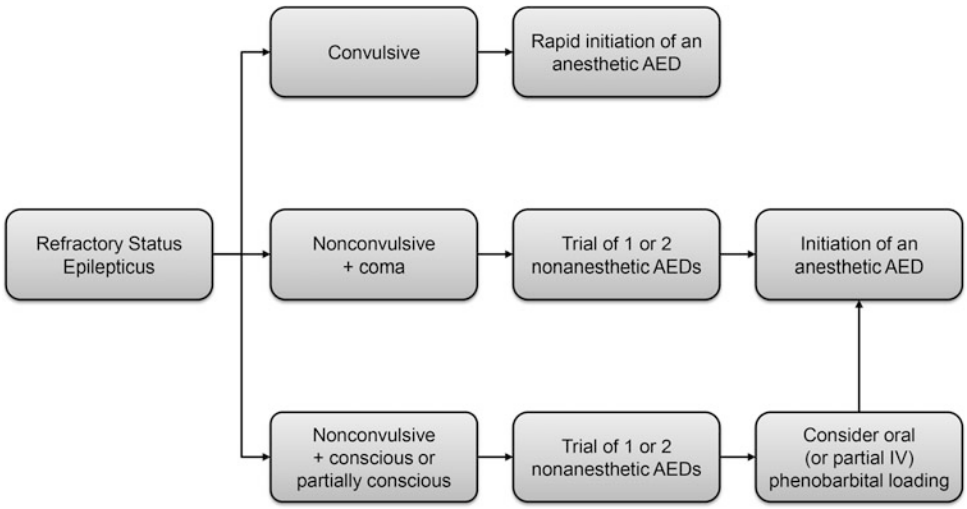

Fig. 17.1 Suggested algorithm for the selection of 3rd–5th *line* anti-seizure drugs for treatment of refractory status epilepticus. *ASD* anti-seizure drug

Table 17.1 Non-anesthetic anti-seizure drug options for the treatment of refractory and super-refractory status epilepticus

Drug	Loading/starting dose	Maintenance dose	Therapeutic level	Adverse effects
Fosphenytoin[d]	18–20 mg PE/kg IV up to 150 mg/min	5–7 PE/kg/day IV, divided every 8 h	Measure phenytoin level	Hypotension, arrhythmia, nonallergic pruritus
Phenytoin[d]	18–20 mg/kg IV, up to 50 mg/min	5–7 mg/kg/day oral/IV, divided every 8 h	Total: 15–20 μg/mL; Free: 1.5–2.5 μg/mL	Hypotension, arrhythmia, metabolic acidosis or tissue injury with extravasation (diluted in propylene glycol)
Valproate[d]	20–40 mg/kg, up to 3 mg/kg/min	30–60 mg/kg/day oral/IV, divided every 6 h	80–140 μg/mL	Hyperammonemia, pancreatitis, thrombocytopenia
Levetiracetam[d]	20–60 mg/kg, up to 500 mg/min	2–12 g/day oral/IV, divided up to every 6 h	25–60 mg/L	Somnolence, rarely agitation
Lacosamide[d]	200–400 mg, over 5 min	400–600 mg/day IV divided every 12 h	Unknown	Mild sedation, allergic skin reactions, prolongation of PR interval
Phenobarbita[a,d]	5–10 mg/kg, up to 60 mg/min	1–4 mg/kg/day oral/IV, divided every 6–8 h	20–50 mg/mL	Sedation, respiratory depression, rare metabolic acidosis due to propylene glycol toxicity
Clonazepam[b,d]	0.015 mg/kg IV	0.5–8 mg/day oral, divided every 6–12 h	Unknown	Mild sedation
Topiramate	200–400 mg oral	400–800 mg/day oral, divided every 8–12 h[c]	Unknown	Metabolic acidosis

IV intravenous; *min* minutes; *PE* phenytoin equivalent
[a]This is a non-anesthetic dose and infusion rate recommendation for the treatment of nonconvulsive SE with some preservation of consciousness. Airway and hemodynamic monitoring including blood pressure and telemetry monitoring are still required
[b]Not available in intravenous form in the United States
[c]Doses up to 1200–1600 mg have been used and are recommended in the Neurocritical Care Society guidelines (Brophy, 2012 [55])
[d]Fast acting intravenous ASD options for the acute control of RSE

additional fast acting non-anesthetic ASDs prior to initiating an anesthetic drug (Table 17.1). When a patient with non-convulsive RSE is comatose, a third line fast acting IV ASD may be administered, followed by a quick assessment of the clinical and electrographic response in order to achieve seizure control as rapidly as possible with escalation to an anesthetic drug if the third line treatment fails. When some preservation of consciousness exists in the setting of non-convulsive seizures, every attempt should be made to avoid the use of anesthetic drugs as long as possible. In these patients, as well as those with a 'do not resuscitate' order, we have had success with loading half or even three-quarters of a full phenobarbital load IV in divided doses, waiting several hours in between. Given the side effect profile of phenobarbital, which includes prolonged sedation, hypotension, and respiratory depression, this is usually considered after failure of multiple non-anesthetic ASDs (i.e., fourth or fifth line treatment). Loading 5 mg/kg of phenobarbital IV followed by another 5 mg/kg load several hours later (if needed) while carefully monitoring the hemodynamic and respiratory status, can be effective and avoid the need for a continuous anesthetic infusion. This should be followed by a maintenance dose of phenobarbital (see Table 17.1).

Drug selection is determined on a case-by-case basis, but important considerations exist. Patients with known epilepsy may respond well to an IV bolus of their chronic maintenance ASD, if available, even if recent levels had been therapeutic in the outpatient setting. Consideration should also be given to common adverse effects and drug interactions. For example, phenytoin and fosphenytoin are best avoided in hemodynamically unstable patients, as they cause clinically significant hypotension in up to 50% of patients during infusion of the loading dose [30, 31]. Valproate may not be the best option in patients previously loaded with fosphenytoin or phenytoin as a second line therapy, because valproate will initially displace the protein bound portion of phenytoin and inhibit its metabolism, thereby increasing the free levels of phenytoin and decreasing the free valproate concentrations [32]. While free phenytoin and valproate concentrations will eventually be normalized when steady state is reached, this interaction may defeat the purpose of attempting rapid control of seizures, avoidance of intubation, and initiation of anesthesia. For a thorough review of the pharmacologic properties, efficacy and safety data for each ASD, see Trinka and colleagues, 2015 [33].

Anesthetic Anti-seizure Drugs

In generalized convulsive status epilepticus, early escalation to anesthetic drugs is justified because rapid seizure control is imperative to avoid the development of pharmacoresistance, neuronal injury, and systemic complications. Commonly used anesthetic ASDs are listed in Table 17.2. There is insufficient evidence to recommend one anesthetic ASD over another [20, 21]. There are three conventional choices —barbiturates (thiopental or its main metabolite, pentobarbital), midazolam, and propofol—although ketamine has become an alternative choice as experience with it has increased. One randomized controlled trial was attempted comparing thiopental and midazolam, but the trial was powered for 150 patients and recruited only 24 [22]. A systematic review of published (primarily uncontrolled) case series reported control of RSE without breakthrough seizures to be 42, 66, and 60%, respectively, for midazolam, propofol, and barbiturates [6].

As there are no randomized or controlled comparative data upon which to differentiate these choices, selection is based primarily on the advantages and adverse effect profile of each drug in relation to the comorbidities of the patient. It should be stated that all anesthetic ASDs are associated with high rates of infection [16, 17]. If an anesthetic ASD is initiated and titrated to typically adequate doses without achieving electrographic seizure control, an alternative anesthetic drug is usually added or substituted. According to recently published data from the global audit of treatment of refractory SE, the most widely used initial anesthetic ASD is midazolam (59%), followed by propofol (32%), and barbiturates (8%) [12].

Midazolam. Midazolam is a benzodiazepine administered via IV infusion which acts by binding to and enhancing the action of the $GABA_A$ receptor. Onset of action occurs within minutes and it is relatively short-acting in non-obese patients with normal renal function (elimination half-life of 1.8–6.4 h). These properties make it ideally suited to prolonged use without accumulation, but accumulation may occur in adipose tissue and with renal insufficiency. Tachyphylaxis may develop, sometimes after only one day of use, necessitating gradually increasing doses to maintain seizure control. The propensity for breakthrough seizures to develop during treatment with midazolam has been shown in multiple studies [34, 35]. As midazolam is a strong respiratory depressant, mechanical ventilation is required, and hypotension requiring pressors occurs in 30–50% of patients [6, 29, 34]. In a systematic review of 28 studies describing 193 patients with RSE, 54 of whom were treated with midazolam, seizures recurred acutely after the loading dose in 20% of cases. Breakthrough seizures occurred after the

Table 17.2 Anesthetic anti-seizure drug options for the treatment of refractory status epilepticus

Drug	Loading dose	Infusion rate	Adverse effects	Special considerations
Midazolam	0.2 mg/kg IV every 5 min until seizures controlled; maximum dose of 2 mg/kg	0.1–2.0 mg/kg/h	Respiratory depression, hypotension	Tachyphylaxis, requires mechanical ventilation, accumulates in adipose tissue and renal insufficiency
Propofol	2 mg/kg IV every 5 min until seizures controlled; maximum dose 10 mg/kg	30–200 mcg/kg/min; Avoid use $\geq$80 mcg/kg/min for $\geq$48 h	Hypotension, propofol infusion syndrome (potentially fatal myocardial failure, lactic acidosis, hypertriglyceridemia, & rhabdomyolysis)	Requires adjustment of daily caloric intake by 1.1 kcal/ml, requires mechanical ventilation
Ketamine	1–2 mg/kg IV every 5 min until seizures controlled; maximum dose 4.5 mg/kg	1.2–7.5 mg/kg/h	Hypertension, hypotension, supraventricular tachycardia, bradyarrhythmias	Requires mechanical ventilation
Pentobarbital	5 mg/kg IV up to 50 mg/min every 5 min until seizures controlled or maximum 15 mg/kg	0.5–5 mg/kg/h	Hypotension, paralytic ileus, respiratory depression, rare hepatotoxicity, rare metabolic acidosis due to propylene glycol toxicity, prolonged sedation	Complete loss of neurological function at high doses, requires mechanical ventilation
Phenobarbital[a]	20 mg/kg IV up to 100 mg/min	1–4 mg/kg/day oral/IV, divided every 6–8 h	Prolonged sedation, respiratory depression, rare metabolic acidosis due to propylene glycol toxicity	Requires mechanical ventilation
Thiopental[b]	2–7 mg/kg IV up to 50 mg/min	0.5–5 mg/kg/h	Hypotension, respiratory depression, paralytic ileus, prolonged sedation	Accumulates in adipose tissue, metabolized to pentobarbital

[a]Included here despite the absence of a continuous infusion as it requires intubation and mechanical ventilation
[b]Not available in the United States

first six hours of treatment in 51%, and withdrawal seizures occurred during weaning of midazolam in 63% [6]. More recently, a study compared 100 patients treated with a high-dose continuous midazolam infusion (median maximum dose 0.4 mg/kg/h, interquartile range (IQR) 0.2–1.0) to 29 historical controls at the same center treated with a lower dose midazolam protocol (median maximum dose 0.2 mg/kg/h, IQR 0.1–0.3) [29]. Withdrawal seizures, occurring within 48 h of drug discontinuation, were less frequent in the high-dose group (15 vs. 64%; odds ratio (OR) 0.10; 95% CI 0.03–0.27) and mortality was lower (40 vs. 62%; OR 0.34; 95% CI 0.13–0.92) compared with those in the low-dose group, despite a higher incidence of hypotension, and similar baseline patient characteristics and duration of midazolam infusion. The results of this study suggest that high doses of midazolam are safe and associated with fewer withdrawal seizures. The implications of the lower mortality are unclear given the historical controls and inability to account for other practice changes.

Propofol. Propofol is an anesthetic with ill-defined anti-seizure properties, which is thought to act by modulation of the $GABA_A$ receptor, and possibly N-methyl-D-aspartate (NMDA) antagonism, at least in vitro [36]. Like midazolam, propofol is very short-acting and has a rapid onset of action. Other advantages include its intracranial pressure and cerebral metabolism lowering properties [37]. Pressors are required for treatment of hypotension in 22–55% of patients [6, 22, 38]. Apnea occurs in 50–84% of patients, and mechanical ventilation is required [39]. The most feared complication of propofol is the propofol infusion syndrome (PRIS), a syndrome of metabolic acidosis, rhabdomyolysis, renal failure, hyperkalemia, hypertriglyceridemia, and rapid cardiovascular collapse which results from a toxic effect on mitochondrial and cellular metabolic function. The incidence of PRIS is unknown, and estimates vary widely with the dose and duration of use [38, 40]. Risk factors include young age, high fat and low carbohydrate intake, concomitant catecholamine infusion or corticosteroid use, and prolonged high-dose infusions ($\geq$80 mcg/kg/min, for $\geq$3 days) [40, 41]. In a study of 31 patients with RSE treated with propofol for a median 67 (range 2–391) hours with median cumulative doses of 12,850 (range 336–57,545) mg, three sudden cardiorespiratory arrests occurred without clear explanation. Two patients died and 11 additional patients exhibited features of PRIS despite careful monitoring for metabolic and cardiac changes [40]. It is therefore likely that the only way to avoid this potentially lethal complication is with the use of a protocol limiting its use to no more than 2 or 3 days at doses not higher than 80 mcg/kg/min. Treatment of PRIS is primarily supportive and includes stopping propofol, supporting the cardiopulmonary and renal systems, sometimes with cardiac pacing, renal replacement therapy, and extracorporal membrane oxygenation [42].

While significant clinical experience exists with propofol, data about efficacy is limited. One study examined the use of propofol in 27 consecutive episodes of RSE retrospectively, and found that breakthrough seizures occurred in 9/27 (33%) episodes, but in only two cases were the seizures severe enough to prompt substitution of an alternative anesthetic ASD [38]. In a systematic review of 28 studies describing 193 patients with RSE, 33 of whom were treated with propofol, seizures recurred acutely after the loading dose in 27% of cases. Breakthrough seizures occurred after the first six hours of treatment in 15%, and withdrawal seizures occurred during weaning in 46% of cases [6].

Barbiturates. Thiopental and its metabolite, pentobarbital, are barbiturate anesthetic drugs with strong anti-epileptic action. Their primary mechanism of action is to enhance transmission at the $GABA_A$ receptor but they also lower the core body temperature and may have neuroprotective effects. The barbiturates have a strong sedative effect and are respiratory depressants, necessitating mechanical ventilation. At high doses, they can result in loss of all brainstem reflexes and an isoelectric EEG, mimicking brain death [43].

Barbiturates are virtually always effective in achieving initial seizure control. Nevertheless, because of their prolonged duration of action, it is this author's opinion that they are not an ideal choice for first-line anesthetic therapy. There is a subset of patients with RSE who require only 24 h of anesthetic therapy and, upon correction of the etiology, are easily weaned from anesthesia, extubated, and discharged from the ICU within a 12–24 h period. If thiopental or pentobarbital is chosen as the first-line anesthetic therapy, the likelihood of the patient awakening and liberation from mechanical ventilation within that time frame is significantly reduced. This is due to their zero order kinetics, rapid redistribution, and resultant accumulation leading to a long half-life, prolonged recovery times [44], and longer duration of mechanical ventilation [22]. The barbiturates are metabolized by the liver, undergo autoinduction, and have many drug–drug interactions. Hypotension requiring pressors occurs in 29–77% [6, 45] of patients [22]. While less common, several other potentially serious systemic complications are specific to barbiturate. A relatively common complication of barbiturate infusions is adynamic ileus (Fig. 17.2), reported in 10% of patients [45]. When severe, bowel ischemia, and even perforation can result [22, 46]. Rarely, lingual edema (Fig. 17.3) can develop risking airway obstruction [47]. This gradually resolves after discontinua-

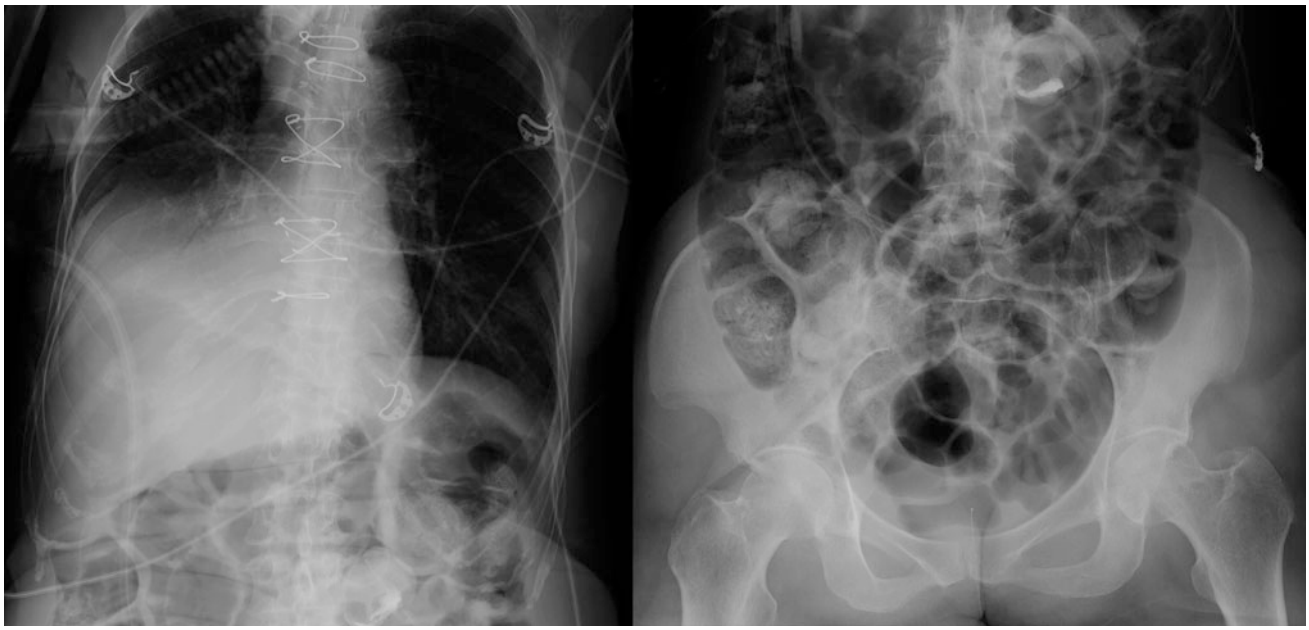

Fig. 17.2 Large amount of small bowel and colonic gas consistent with ileus in a patient treated with a continuous pentobarbital infusion for 17 days at a maximum dose of 5 mg/kg/h

tion of the drug. In <1% of patients, propylene glycol toxicity may develop which manifests as a progressive acidosis that resolves after drug discontinuation [45]. Rarely, pancreatic, gastric, or hepatic injury may develop due to systemic and splanchnic hypoperfusion, complications which more commonly occur in elderly patients [48].

In a retrospective review of 31 patients with SRSE treated with pentobarbital infusions, seizure control was achieved in 90% of patients but recurred in 48% upon weaning of the drug [45]. A systematic review of 28 studies describing 193 patients with RSE, 106 of whom were treated with pentobarbital, seizures recurred acutely after the loading dose in only 8% of cases. Breakthrough seizures occurred after the first six hours of treatment in 12%, and withdrawal seizures occurred during weaning in 43% of cases [6].

Ketamine. Ketamine is an NMDA antagonist—a potential advantage over the other anesthetic ASDs, as prolonged seizures are accompanied by pharmacoresistance to GABA agonists [49] but not to NMDA antagonists [50]. An additional advantage is its lack of respiratory depressant effects. Onset of action occurs within seconds, and it is relatively short-acting (elimination half-life of 2–3 h). Metabolism is hepatic and excretion is largely renal. Efficacy has been demonstrated in animal models, even in late stages of RSE [50, 51]. Experience in humans with RSE has been increasing in recent years. The largest published series is a multicenter retrospective review of 46 adults and 12 children totaling 60 episodes of RSE treated with ketamine [52]. In this series, ketamine was thought to have contributed to permanent control of RSE in 32% of cases, and transient control in an additional 13%, similar to the reported efficacy of the other anesthetic ASDs [6]. Interestingly, response rate was highest when ketamine was introduced early (as a third or fourth line agent). Still, an assessment of efficacy in a retrospective fashion, without controlling for the effects of other ASDs, treatment of the cause of RSE, and other factors, is questionable. The true value of this study lies in its confirmation of relative safety at the reported doses. Infusions of up to 10 mg/kg/h for up to 27 days were not associated with increased complications or mortality compared to patients receiving lower doses for fewer days [52]. Two patients in this series developed supraventricular tachycardia that resolved after drug discontinuation. One developed atrial fibrillation requiring amiodarone, and there was one incident of severe acidosis during coadministration of both high-dose midazolam and ketamine leading to discontinuation of the drug. Despite a call for earlier use [53], it is generally reserved for the most severe cases, usually after more than one anesthetic ASD has failed [50], a practice which is in line with current guidelines [54].

Treatment Goals

Once an anesthetic ASD has been initiated, the primary treatment goals are clinical and electrographic seizure suppression, and reversal of the cause of seizures. It is a common practice to titrate anesthetic ASDs to a predetermined EEG endpoint. Endpoints are controversial, and available evidence is conflicting [8, 10, 29, 55]. Options include

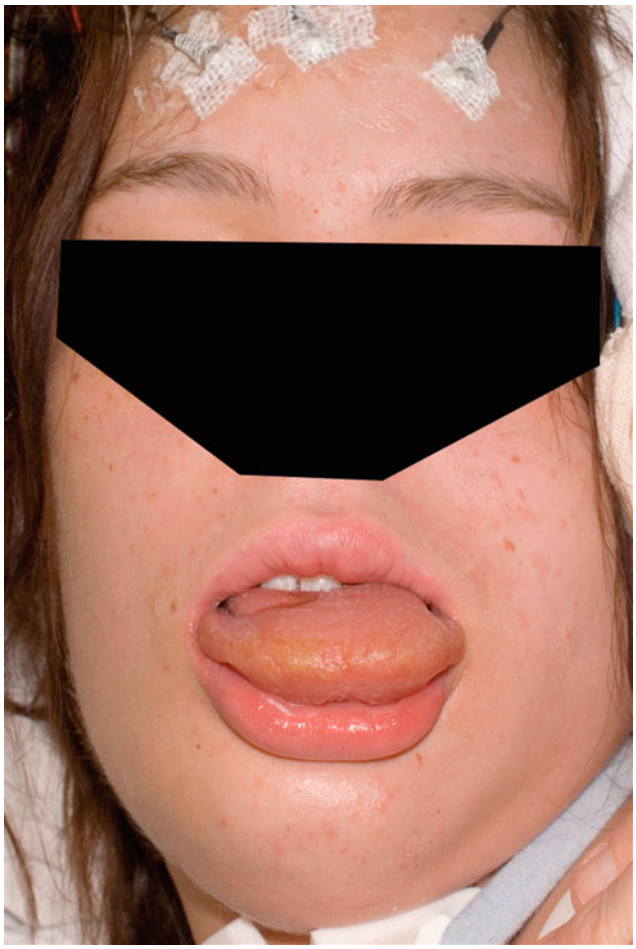

Fig. 17.3 Photograph of an enlarged tongue in a 20-year-old woman with refractory status epilepticus treated with continuous pentobarbital infusion for two weeks with a maximum dose of 9 mg/kg/h. From Ji et al. [48] with permission

complete background suppression (sometimes referred to as 'isoelectric' or 'flat'), burst suppression, or seizure suppression. Determining how much to suppress requires a clinical judgement that balances the risks of increased suppression (very high doses of anesthetic ASDs are sometimes required to achieve a burst suppression or isoelectric EEG background, risking increased hypotension, and other systemic complications), with the benefit of increased seizure suppression. Continuous EEG monitoring has shown that seizures may still emerge from a burst suppression pattern, so it follows that greater suppression should confer better seizure control [56].

Next Steps

Once achieved, it is standard practice to maintain the desired EEG endpoint for 24–48 h prior to a slow withdrawal of anesthetic ASDs [54]. Prior to attempting the first anesthetic wean, 2–3 non-anesthetic ASDs (usually including the drug selected as second line therapy) should be initiated at high doses and titrated to achieve therapeutic levels. In patients at risk for development of adynamic ileus (i.e., patients receiving opiates or barbiturates), the IV route of administration is preferred to ensure reliable absorption. In other patients, ASDs may be administered enterally via a nasogastric or orogastric tube. No evidence exists to guide optimal ASD combinations in this setting. General considerations for drug selection include seizure type, systemic comorbidities, drug–drug interaction profiles, and avoidance of polypharmacy (>3 ASDs may add morbidity by increasing the risk of adverse effects without evidence of benefit).

In addition, the clinician must ensure that the underlying etiology has been addressed. By this time patients will have undergone at a minimum, a thorough history, noncontrast head computed tomography (CT) scan, comprehensive laboratory evaluation, and lumbar puncture for cerebrospinal fluid (CSF) analysis. If an etiology is identified, attempts are made to correct the etiology (e.g., reverse hypoglycemia), or at least initiate appropriate treatment when the etiology is not expected to resolve rapidly (e.g., fulminant bacterial meningitis). If an etiology has not yet been identified at this stage, this is the time to begin the search for more unusual causes of SE (e.g., complete autoimmune encephalopathy panels including NMDA receptor, and voltage gated potassium channel antibodies) and to consider initiation of empiric immunotherapy. (See also Chap. 8, "Unusual Causes of Status Epilepticus.")

Weaning of Anesthesia

There is no evidence to guide the weaning of an anesthetic ASD. This author's practice is to wean anesthetic drugs one at a time by 10% per hour. For example, if the desired EEG endpoint is achieved with midazolam 20 mg/h and propofol 50 mcg/kg/min, and maintained for 24–48 h, the midazolam dose would be decreased by 2 mg/h each hour until off, while carefully monitoring the EEG for seizure recurrence. When midazolam is successfully discontinued, the propofol wean would begin, decreasing the dose by 5 mcg/kg/min every hour until off. Deciding which anesthetic drug to wean first is somewhat arbitrary but clinical circumstances may dictate which drug to wean first. Patients exposed to prolonged barbiturate infusions are at higher risk for withdrawal seizures; this may be avoided by utilizing phenobarbital as one of the 2 or 3 non-anesthetic ASDs [57].

If seizures recur, usual practice is to resume anesthesia and reestablish EEG suppression. Occasionally breakthrough seizures that occur upon weaning of anesthesia will subside spontaneously. How long to observe, if at all, remains a clinical judgment. It is probably reasonable to

observe and allow some electrographic seizures during an anesthetic wean, but if the frequency of breakthrough seizures does not decline gradually over time, anesthesia should be resumed. The same principle applies to other patterns that do not meet criteria for electrographic seizures, but are on the ictal–interictal continuum. As long as the EEG background continues to improve, and seizures are infrequent and declining in frequency, this author's practice is to continue weaning. During this time, bolus doses of benzodiazepines and further optimization of the patient's non-anesthetic ASD regimen may increase the likelihood of successful weaning.

Super-Refractory Status Epilepticus

If seizures continue or recur 24 h or more after the initiation of anesthetic therapy, the patient is considered to have reached the stage of 'super-refractory status epilepticus.' The majority of recommendations to guide treatment of this stage come from expert consensus. Issues that remain unresolved include what anesthetic drug to choose after failure of a weaning attempt and when to attempt weaning again. Barbiturates are often used as second line anesthetic ASDs [12]. They are reasonably well suited for long term use and are not prone to tachyphylaxis. Over time, the time between weaning attempts is increased, and after failure of several attempted weans, anesthesia is often continued for 5–7 days between weaning attempts.

Between Weaning Attempts

If not already accomplished, the primary focus between weaning attempts must be on identification and treatment of the seizure etiology. Additional tasks include careful temperature control, continued optimization of the non-anesthetic ASD regimen, and meticulous daily screening for complications of critical illness and anesthetic ASD use. Common complications in this setting include infections (especially pneumonia), venous thromboembolism, skin breakdown with formation of decubitus ulcers, adynamic ileus, and anasarca. Cardiac complications are not infrequent and include arrhythmias and stress-induced cardiomyopathy [58]. Excellent nursing and use of a 'checklist mentality' can aide in early recognition (or even prevention) of these complications.

Treatment of Antibody-Mediated or Cryptogenic Refractory Status Epilepticus

When a patient presents with a history suggestive of autoimmune or paraneoplastic disease (e.g., delirium, mood change, memory and personality disturbance, and focal seizures with or without secondary generalization), initiation of immunotherapy is indicated as soon as metabolic, toxic, infectious, and structural etiologies have been excluded (by basic laboratory evaluation and noncontrast CT scan), *and* the CSF cell count, chemistry, and gram stain are not suggestive of infection, whether or not an antibody has been identified. In the absence of such a history or other markers of inflammation or autoimmunity, it is appropriate to await negative CSF cultures and serologies prior to a trial of immunotherapy.

Clinical features supportive of immune mediated SE include: (1) a well-defined clinical syndrome (e.g., limbic encephalitis or faciobrachial dystonic seizures), (2) subacute onset (maximal seizure frequency <3 months) of cryptogenic epilepsy, (3) cryptogenic RSE or new onset refractory status epilepticus (NORSE), (4) a viral prodrome, (5) antecedent psychiatric symptoms, (6) history of systemic autoimmunity, or (7) history of neoplasia. Supportive paraclinical features include: (1) evidence of central nervous system inflammation (e.g., CSF pleocytosis, elevated CSF protein, CSF oligoclonal bands, elevated CSF IgG index or synthesis rate, mesial temporal or parenchymal T2-weighted or fluid-attenuated inversion recovery sequence hyperintensities, or hypermetabolism on functional imaging), (2) extreme delta brush pattern on EEG, or serologic markers of systemic autoimmunity (e.g., antinuclear antibody or thyroid peroxidase antibody positivity) [59]. These patients should undergo comprehensive evaluation for neural-specific autoantibodies in the serum and CSF.

Multiple arguments in favor of early empiric initiation of immunotherapy in SRSE can be made. First, earlier initiation of immunotherapy confers a better outcome in autoimmune central nervous system diseases when compared with delayed initiation of therapy [60–62]. Second, autoimmune and paraneoplastic syndromes are the most common cause of cryptogenic RSE [63], also known as NORSE [64]. Finally, there is increasing evidence that inflammation plays an important role in epileptogenesis and activation of specific inflammatory signaling pathways (e.g., interleukin-1 receptor/toll-like receptor (IL-1R/TLR) pathway) [65–68].

A trial of immunotherapy usually consists of high-dose IV steroids alone or combined with either plasma exchange or IV immunoglobulin [69]. If an antibody is identified, or the patient responds favorably to the trial of immunotherapy as evidenced by fewer breakthrough seizures or reduction in the dose of anesthesia required to maintain the desired EEG suppression target, immunosuppression should be continued (Table 17.3). If there is no objective favorable response to the trial of immunotherapy but an antibody-mediated syndrome is proven or strongly suspected, consider a second immunotherapy trial with an alternative agent. In patients where an antibody is identified, and patients in whom the etiology remains unknown even after an exhaustive evaluation, escalation of immunotherapy to rituximab or cyclophosphamide can be considered when there is either no, or incomplete, response to first-line treatments [59].

While this approach remains unproven in undifferentiated NORSE, experience with 501 patients with anti-NMDA receptor encephalitis demonstrated that rituximab and cyclophosphamide are usually effective in patients who do not respond to first-line immunotherapies [70]. A series of five patients with NORSE reported better outcomes with earlier initiation of immunotherapy compared with delayed initiation [71]. Recognizing the limitations inherent in case reports and series, this further supports the notion that early immunotherapy may be beneficial in cases of SRSE where no cause has been identified.

Finding a neural-specific autoantibody should prompt a targeted search for malignancies associated with the specific antibody [72]. When no antibody is identified, but an antibody-mediated syndrome is suspected, it is appropriate to screen broadly for malignancy by obtaining a CT scan of the chest, abdomen, and pelvis and if negative, proceed to fluorodeoxyglucose positron-emission tomography (FDG PET)-CT [73]. FDG PET is not sufficient in women with NMDA receptor encephalitis or in any patient suspected of having a germ-cell tumor. In these situations, ultrasound and MRI are the preferred modalities [59]. When initial malignancy screening is negative, ongoing surveillance may be required.

'Hail Mary' Pharmacologic Therapies

A number of other pharmacologic options have been reported and can be considered 'when all else fails' (Table 17.4). Experience with these drugs in the setting of SRSE is limited to case reports and small case series. Each of these therapies has limited evidence of benefit and either unknown, or at least moderate risk. They should therefore be

Table 17.3 Acute immunotherapy options in antibody mediated or cryptogenic refractory status epilepticus

Drug	Route	Dose	Schedule
Methylprednisolone	Intravenous	1000 mg	Daily for 3–5 days; then weekly for 4–6 weeks
Immune globulin	Intravenous	0.4 g/kg	Daily for 5 days; then weekly for 4–6 weeks
Plasma exchange	Intravenous	1 exchange	Every other day for 10–14 days
Rituximab	Intravenous	375 mg/m^2	Weekly for 4 doses
Cyclophosphamide	Intravenous	500–1000 mg/m^2	Monthly for 3–6 months
	Oral	1–2 mg/kg	Daily

Table 17.4 'Hail Mary' pharmacologic options for the treatment of super-refractory status epilepticus

Drug	Route	Dose	Level	Adverse effects
Magnesium	IV	LD: 2–4 g over 2 h; Maintenance: 2 g every 8 h or 0.5–2 g/h infusion	2.0–3.5 mEq/L (up to 7.0 mEq/L)	Respiratory depression at levels of 5.0–6.5 mEq/L; Cardiac conduction abnormalities at levels >7.5 mEq/L
Lidocaine	IV	LD: 1–5 mg/kg every 5 min until seizures controlled; Maintenance: up to 6 mg/kg/h	<5 mg/L	Mild hypotension
Etomidate	IV	LD: 0.3 mg/kg every 5 min until seizures controlled; Maintenance: 1.2–7.2 mg/kg/h	Unknown	Tachyphylaxis, adrenal insufficiency, hypotension
Isoflurane	Inhaled gas	End tidal anesthetic concentration titrated to desired suppression of the seizure and EEG background activity	MAC 1.2–5.0%	Hypotension, adynamic ileus, possible neurotoxicity with prolonged use
Felbamate	Oral	LD: 400 mg every 8 h; Maintenance: up to 1200 mg every 8 h	40–100 2 g/mL	Aplastic anemia, hepatic failure

LD loading dose, *IV* intravenous, *MAC* minimum alveolar concentration

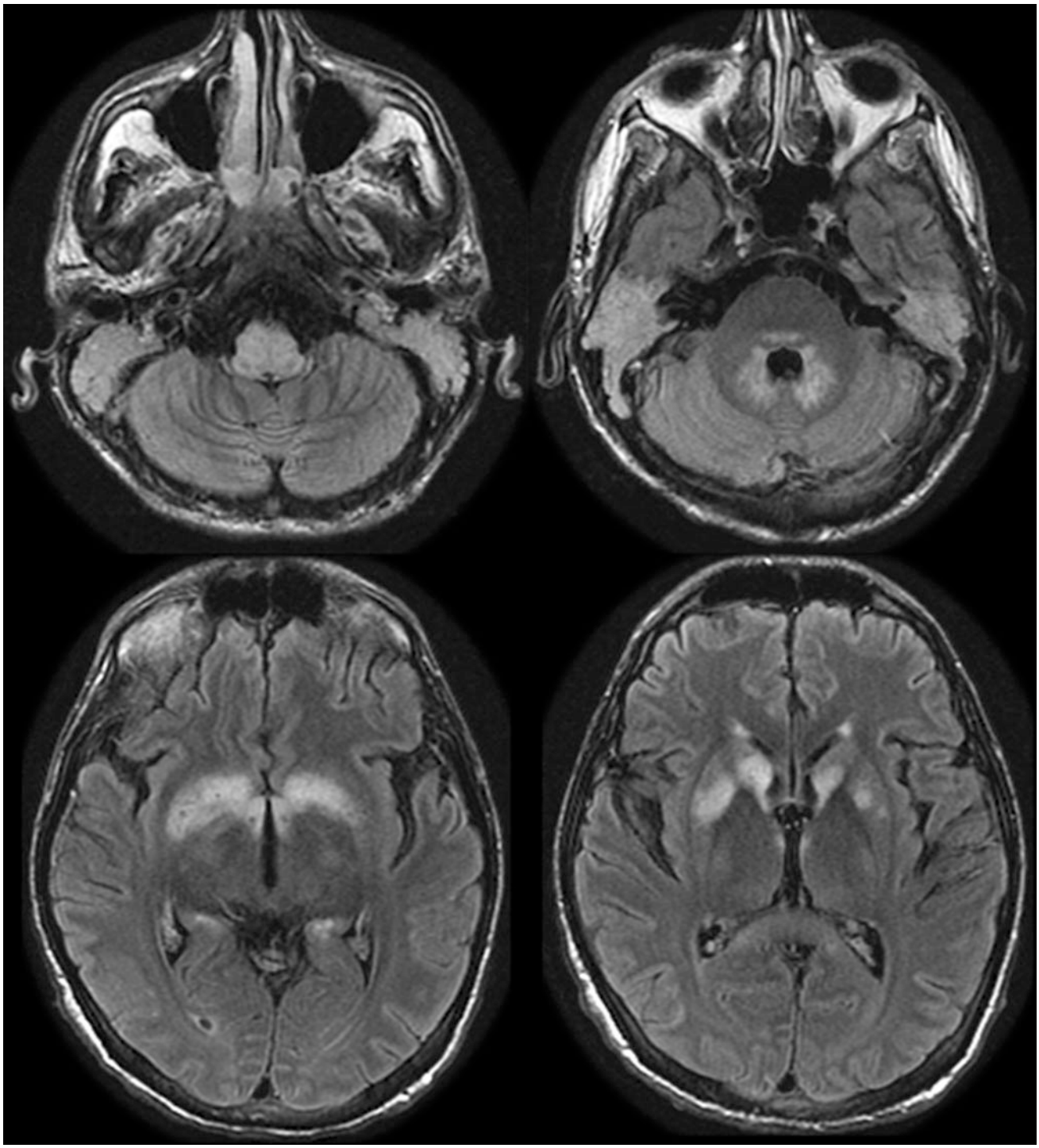

Fig. 17.4 Axial brain magnetic resonance images with fluid-attenuated inversion recovery sequences showing hyperintensities in the medulla, periventricular cerebellum, and basal ganglia after prolonged treatment with isoflurane

considered only in the most refractory cases when other options have proven unsuccessful.

Inhalational Halogenated Anesthetics. The inhalational halogenated anesthetic drugs isoflurane and desflurane have been used to treat RSE, with variable success. A recent literature review reported 13 studies with 28 adult patients treated with inhalational anesthetics in which electrographic seizure control was achieved in 26 (92.9%) patients. Isoflurane was used in the majority of cases, and the most common complication was hypotension requiring

vasopressor support [74]. In one series of 7 patients treated with inhalational anesthetic drugs, anesthesia was maintained for a mean of 11 days (range 2–26), and four patients had good outcomes (Glasgow Outcome Scale score of 4–5) while three patients died [75]. Complications included hypotension (7/7), atelectasis (7/7), infections (5/7), paralytic ileus (3/7), and deep venous thrombosis (2/7). MRI changes in the basal ganglia, cerebellum, and brainstem have been reported after prolonged use of isoflurane in two patients (Fig. 17.4) [76]. These changes were reversible with discontinuation of the drug but cannot be entirely separated from possible brain injury due to the excitotoxic state induced by SRSE.

Lidocaine. Lidocaine has been reported for use in SRSE where it is used as a continuous anesthetic infusion. A recent systematic review reported 11 published manuscripts and two abstracts covering 76 adult patients treated for 82 episodes of SE [77]. Lidocaine doses varied with some receiving only bolus doses and others receiving a combination of boluses and continuous infusion IV lidocaine. Seizure control was reported in 53 of 82 (64.6%) episodes with a >50% reduction in seizure frequency reported in an additional 5 (6.1%) episodes. Seizures recurred upon withdrawal of lidocaine in 13 of 58 (22.4%) of those who were initially responsive to lidocaine. Lidocaine was generally well tolerated, but two patients died from cardiorespiratory arrest during lidocaine infusion.

Magnesium. Experimental evidence for the benefit of IV magnesium in non-eclamptic status epilepticus is contradictory [78, 79]. It has been tried in humans, with favorable responses reported [80]. A recent systematic review of magnesium sulfate for non-eclamptic SE found 19 published papers reporting 28 patients of whom 11 were adults, 9 were children, and 8 were of unknown age. Seizure reduction or control occurred in half of the published cases, but in half of those, seizures recurred upon withdrawal of magnesium therapy. Complications included one patient who developed limb weakness and two who developed heart block [81].

Felbamate. Felbamate was approved by the US FDA for treatment of partial seizures with or without secondary generalization in 1993. While its exact mechanism is not known, it acts as an antagonist at the strychnine-insensitive glycine recognition site of the NMDA receptor–ionophore complex [82].Animal studies have shown that felbamate may increase the seizure threshold and decrease seizure spread [83]. Due to two rare but serious idiosyncratic effects of felbamate, aplastic anemia, and hepatic toxicity, its use has been restricted and a 'Black Box' warning was inserted into packaging. Despite the risks, in cases of SRSE where safer ASDs have failed, felbamate remains an option. If initiation of felbamate is considered, it should be with the guidance of an epileptologist, and with frequent monitoring of blood cell counts and liver function [84]. In a series of 63 consecutive episodes of SRSE, felbamate was the last drug added prior to successful weaning of anesthesia in two cases where it was added as the 9th and 11th attempted ASD (including anesthetic and non-anesthetic drugs) [10].

Allopregnanolone. Allopregnanolone is a neurosteroid metabolite of progesterone with anticonvulsant properties in multiple animal seizure models [85–88]. Infusion of allopregnanolone was reported to be successful in a very refractory case of pediatric SE [89]. A phase II clinical trial of allopregnanolone (SGE-102), has been completed [90] and a multicenter blinded randomized controlled trial is ongoing (ClinicalTrials.gov Identifier: NCT02477618).

Conclusions

Nearly all cases of SRSE can be controlled with anesthetic ASDs, but these drugs are not a panacea. Control of the underlying cause of the seizures and multiple non-anesthetic ASDs at high therapeutic levels are required to achieve liberation from anesthesia. In patients with NORSE or proven antibody-mediated encephalitis, early initiation of immunosuppression is recommended. Equally important is the careful maintenance of normal organ function and early identification and management of systemic complications to decrease the ultimate morbidity for those patients who do survive and often face a difficult and frequently prolonged recovery.

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Nonpharmacologic Treatments of Status Epilepticus

18

Mackenzie C. Cervenka

Introduction

As described in prior chapters, status epilepticus is the second most common neurologic emergency world-wide (second only to stroke) and occurs in as many as 10–41 per 100,000 individuals annually [1]. Prospective randomized clinical trials have established the efficacy of benzodiazepines as first-line treatment, and large randomized trials are ongoing to determine the most appropriate second-line antiseizure drug. Nearly half of patients do not respond to first- and second-line treatments and are diagnosed with "refractory" status epilepticus [2]. The term "super-refractory status epilepticus" is used to describe cases in which patients with refractory status epilepticus have recurrence or lack of control of electrographic status epilepticus (convulsive or nonconvulsive) after 24 h of aggressive administration of intravenous anesthetic drugs (e.g., propofol, midazolam, pentobarbital, or ketamine) to suppress seizure activity, followed by an attempt to taper the anesthetic drug [3]. Morbidity and mortality, as well as length of intensive care unit and hospital stays, increase dramatically in patients with refractory status epilepticus (mortality rates exceed 50% in some studies of super-refractory status epilepticus), and prospective evidence-based guidance supporting additional drug trials is scarce.

Increasingly, intensivists are turning to nonpharmacologic therapies to treat status epilepticus once standard antiseizure drugs fail. Among these therapies, therapeutic hypothermia (TH); neurostimulation procedures such as repetitive transcranial magnetic stimulation (rTMS), electroconvulsive therapy (ECT), and vagus nerve stimulation (VNS); intracranial neurosurgical procedures, including seizure focus resection, corpus callosotomy, and multiple subpial transection; and ketogenic diet therapies, including the ketogenic diet, the modified Atkins diet (MAD), and low glycemic index treatment (LGIT) have been most widely used. The majority of the evidence supporting the use of these treatments is derived from studies of animal models of status epilepticus and case reports and case series in humans with *epilepsia partialis continua* (focal motor seizures that recur every few seconds to minutes and are very rare and difficult to control [4]) and in patients with refractory and super-refractory status epilepticus.

M.C. Cervenka (✉)
Department of Neurology, The Johns Hopkins Hospital,
600 North Wolfe Street, Meyer 2-147,
Baltimore, MD 21087, USA
e-mail: mcerven1@jhmi.edu

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Therapeutic Hypothermia

Background

The use of hypothermia in the treatment of human neurologic disease (brain and spine) during neurosurgical procedures was first described in the 1960s [5, 6]. These procedures included "local" of "focal" cooling and "regional hypothermia" with extravascular perfusion. Other techniques employed "surface cooling" and "intravascular perfusion." The basic assumption was that cooling reduced nervous tissue edema and oxygen consumption.

Current studies of hypothermia typically reference "mild" hypothermia (32–36 °C) [7–9], but others have introduced "moderate" hypothermia (30–31 °C) [10] in humans, particularly in children [10]. "Deep hypothermia" (20–30 °C) is typically used in animal models examining mechanisms of action and efficacy of TH for status epilepticus [11–13].

Mechanism(s) of Action

In vitro models, TH has been shown to slow nerve conduction velocity [14, 15] (Table 18.1). In animal models of status epilepticus, TH has been shown to have anticonvulsant properties alone or in combination with intravenous diazepam [16]. Using a pilocarpine and lithium animal model of status epilepticus, investigators also demonstrated reduction

Table 18.1 Mechanisms of action of nonpharmacologic treatments of status epilepticus

	GABAergic	Anti-inflammatory	Slowing of nerve conduction velocity	Disruption of epileptogenic network	Neuro-protective
Therapeutic hypothermia		X	X		X
Neurostimulation					
ECT	X				X
rTMS	X				
VNS	X				
Neurosurgery				X	
Ketogenic diets	X	X			

GABA γ[gamma]-aminobutyric acid
ECT electroconvulsive therapy
rTMS repetitive transcranial magnetic stimulation
VNS vagus nerve stimulation

in neuronal injury in hypothermic compared to normothermic animals [12]. In a second study, animals pretreated with hypothermia prior to pilocarpine-induced status epilepticus did not show the same alterations in concentration of neurotransmitters (glutamate, and γ[gamma]-aminobutyric acid, or GABA) seen in normothermic animals [17], suggesting a potential neuro-protective or antiepileptogenic effect.

In humans, TH is hypothesized to have a neuro-protective effect, in particular in neonates with hypoxic-ischemic encephalopathy and children with traumatic brain injury, by reducing blood–brain barrier permeability, neuroinflammation, and excitotoxicity, which in turn decrease apoptosis and exacerbation of status epilepticus [18].

Treatment Algorithms

Case reports and case series using TH typically describe the use of mild hypothermia induced with the placement of external gel pads and circulating sterile water [14]. This may include an "induction phase" of up to 8 h in which the body temperature is decreased gradually, followed by a "maintenance phase" of 24 h. Urinary bladder and rectal probes are used to monitor body temperature, although monitoring with a pulmonary artery catheter has also been described [10]. Rewarming to normothermia is performed at a rate of 1 °C every 3–4 h [10]. Animal and human studies of hypothermia in status epilepticus have reported success in combination with benzodiazepines or barbiturates, or with ECT [10, 19, 20] (Table 18.2).

"Local" or "focal" cooling is a procedure used intra-operatively during brain surgery in which epileptiform activity is suppressed with the application of cold saline directly to the cortical surface in the location that the epileptiform activity is identified [21].

Evidence for Efficacy

A recent review of the literature identified 13 studies (including 10 original articles and 3 meeting abstracts) reporting 40 patients treated with TH for refractory status epilepticus [22]. The authors found that the average cooling temperature was 33 °C, with external cooling in the majority of cases. Cessation of status epilepticus was reported in 63% of cases, with reduction in seizure activity in additional 15% (Table 18.3).

Side Effects and Adverse Events

Most commonly reported adverse events with TH include shivering, deep venous thrombosis, coagulopathy, and infections [9, 22] (Table 18.4). Patients are noted to have mild bradycardia and hypotension during TH that resolve with fluid resuscitation but can potentially exacerbate hemodynamic instability produced by simultaneous chronic intravenous anesthesia [14]. A recent study suggests that a prospective trial of TH in pediatric refractory status epilepticus is feasible given the substantial number of patients presenting with this illness [23].

Neurostimulation

Background

Neurostimulation has been studied for decades as a treatment for refractory seizures and has been utilized in various forms in the treatment of refractory and super-refractory status epilepticus. These have included ECT, rTMS, and VNS.

Table 18.2 Treatment algorithms for nonpharmacologic treatments of status epilepticus

	Treatment algorithm/technique	Parameters	Comments
Therapeutic hypothermia	Mild hypothermia Moderate hypothermia Deep hypothermia	32–36 °C 30–31 °C 20–30 °C	Typically in adults Typically in children Typically in animals
Neurostimulation			
ECT	Vary with regard to electrode placement	Vary by number and frequency of treatment sessions, current applied, charge, pulse frequency, pulse width	
rTMS	Circular coil Figure-of-eight coil	Vary by coil position, stimulation frequency, duration, intertrain interval, number of sessions, number of stimuli	
VNS		Vary by current output, frequency, pulse width, on and off times	FDA approved for children over 12 years and adults with medically resistant focal epilepsy
Neurosurgery	Focal cortical resection Hemispherectomy Multiple subpial transection Corpus callosotomy	Functional or anatomical Partial or complete	
Ketogenic diets	Classic ketogenic diet Modified Atkins diet Low glycemic index treatment	± fasting followed by 4:1 or 3:1 ratio fat to carbohydrates and protein combined 10–20 g of net carbohydrates per day limit 40–60 g of net carbohydrates per day with glycemic index <50	Most often by enteral formula, but intravenous administration has also been reported

ECT electroconvulsive therapy
rTMS repetitive transcranial magnetic stimulation
VNS vagus nerve stimulation
FDA U.S. food and drug administration

Table 18.3 Efficacy of nonpharmacologic treatments of status epilepticus

	Number of studies	Number of cases	Cessation of status epilepticus (%)
Therapeutic hypothermia	13	40	63
Neurostimulation			
ECT	14	19 (4 children, 15 adults)	37
rTMS	11	21 (8 children, 13 adults)	48[a]
VNS	17	28 (18 children, 10 adults)	76
Neurosurgery	16	51	94
Ketogenic diets	14	52 (37 children, 15 adults)	83

[a]Includes cases with *epilepsia partialis continua*
ECT electroconvulsive therapy
rTMS repetitive transcranial magnetic stimulation
VNS vagus nerve stimulation

ECT was introduced as a possible treatment for epilepsy in the 1930s [24] but was used primarily to treat depression and other psychiatric disorders. The earliest case reports of ECT being used in the treatment of status epilepticus were first published in the 1990s [25–27]. The vagus nerve stimulator was first approved by the U.S. Food and Drug Administration for the adjunctive treatment of medically resistant focal epilepsy in patients over 12 years of age in

Table 18.4 Side effects, serious adverse events, and contraindications with nonpharmacologic treatments of status epilepticus

	Side effects	Reported serious adverse events
Therapeutic hypothermia	Shivering, coagulopathy, bradycardia, hypotension, infection	Deep venous thrombosis
Neurostimulation		
ECT	Memory loss, confusion, seizures, muscle soreness	Status epilepticus
rTMS	Seizures, headache, dizziness, local skin irritation, involuntary movements, transient vision loss	Bradycardia leading to asystole
VNS	Skin irritation, hoarseness, cough, voice changes, throat pain, difficulty swallowing, chest or abdominal pain	Apnea
Neurosurgery	Pain, infection, weakness, hemiparesis (hemispherectomy), aphasia, disconnection syndrome (corpus callosotomy)	Death due to anesthesia reaction, hydrocephalus, intracranial hemorrhage
Ketogenic diets	Constipation, nausea, vomiting, elevated fasting lipids	Fatal propofol infusion syndrome

ECT electroconvulsive therapy
rTMS repetitive transcranial magnetic stimulation
VNS vagus nerve stimulation

1997 and was first described in the treatment of status epilepticus in 2001 [28]. Meanwhile, repetitive transcranial magnetic stimulation was used beginning in the early twenty-first century to treat conditions such as chronic pain, depression, movement disorders, and epilepsy [29]. rTMS was proposed as a treatment for *epilepsia partialis continua* in the mid-2000s [30–32] and specifically for refractory focal status epilepticus in the past few years [33, 34].

Mechanisms(s) of Action

Many mechanisms of action have been proposed in explaining the effectiveness of neurostimulation techniques in interrupting status epilepticus (see Table 18.1). In a kainic-acid animal model of status epilepticus, ECT was shown to prevent neuronal apoptosis [35]. Researchers also propose that ECT may enhance γ[gamma]-aminobutyric acid (GABA) transmission [36] leading to elevation in seizure threshold [37]. Likewise, human studies of VNS have shown possible inhibitory mechanisms including an increase in $GABA_A$ receptor density after 1 year of treatment [38] and increase in cerebrospinal fluid GABA concentrations [39]. In rodent kindling models, studies have demonstrated that rTMS prevented CA1 pyramidal neuron hyperexcitability [40] and increased cortical inhibition [41], suggesting a possible antiepileptogenic effect.

Treatment Algorithms

A variety of treatment algorithms have been described in the implementation of ECT, VNS, and rTMS in refractory and super-refractory status epilepticus (see Table 18.2). With ECT, these treatment algorithms vary with regard to electrode placement, frequency and duration of therapy, and stimulation parameters. Case reports and case series have described electrode placement over bitemporal, bilateral frontocentral, bifrontotemporal, or right frontotemporal and left parietal head regions. The frequency of treatment sessions also varies, most commonly one session per day for one week, with as many as three sessions per day and treatment duration as long as 3 months [24, 37]. ECT treatment regimens also vary widely by stimulation parameters including current applied (milli-Amperes), charge (milli-Coulombs), pulse frequency (Hertz), and pulse width (milliseconds).

VNS parameters used in the treatment of status epilepticus vary with regard to current output during routine stimulation delivery and magnet swipe (0.25–3 mA), frequency (20–30 Hz), pulse width (250 or 500 μS), and on (7–30 s) and off (60 s–5 min) times [42]. Treatment strategies using rTMS also vary between published studies with regard to coil shape ("circular" versus "figure-of-eight" coil), coil position, stimulation frequency, duration, intertrain interval, number of sessions, and number of stimuli [43].

Evidence for Efficacy

In a recent review of treatment for refractory status epilepticus with ECT, 19 patients (15 adult, four pediatric) were reported in 14 studies [37]. Thirty-seven percent had complete seizure resolution, and 21% had significant improvement. Ultimately, over half of patients were dead or severely disabled at the conclusion of these studies (see Table 18.3).

A study reviewing seven published manuscripts and 10 meeting abstracts on VNS for the treatment of refractory status epilepticus identified a total of 28 patients (18 children, 10 adults). These included one prospective cohort study and six retrospective case reviews or case series. In patients diagnosed with refractory generalized status epilepticus, 76% had sustained cessation of status with VNS, as did 25% of patients with refractory focal status epilepticus [42].

A review of studies using rTMS evaluated 11 studies of 21 patients (13 adults, eight children) [34]. The majority of these studies reported patients with epilepsia partialis continua. Forty-eight percent of patients had seizure resolution, and an additional 24% had significant reduction in seizure frequency.

Side Effects and Adverse Events

The most commonly reported side effect of ECT is memory loss that is typically transient but can be persistent [44–46] (see Table 18.4). While ECT has been proposed as a possible treatment for refractory status epilepticus, several publications also document status epilepticus caused by ECT [47–61]. Repetitive transcranial magnetic stimulation has also been reported to provoke seizures in patients with epilepsy [43], although this is very uncommon. Therefore, further studies examining the optimal stimulation parameters to stop seizures and status are necessary. Other reported side effects from rTMS have included headache, dizziness, local skin irritation, involuntary motor activity, and transient vision loss [62]. Among case reports and case series describing the use of VNS for the treatment of refractory status epilepticus, the only reported serious adverse event was bradycardia leading to asystole that responded to resuscitation [42]. Common side effects of VNS insertion include problems related to vagus nerve irritation including hoarseness, cough, voice changes, throat pain, and difficulty breathing or swallowing, as well as chest or abdominal pain, nausea, and headache.

Intracranial Neurosurgery

Background

Several neurosurgical procedures have been employed to reduce or eliminate seizures and have been adopted in some patients with refractory and super-refractory status epilepticus. In patients with focal or partial epilepsy in whom an identifiable lesion is present and is confirmed to be the seizure focus, lesionectomy may be performed. In the absence of a clear abnormality on neuroimaging, surgery may be guided by findings on scalp or intracranial electroencephalography (EEG) or both. Neurosurgical procedures (excluding implantation of stimulation devices, which have been discussed in the previous section) that have been described to treat status epilepticus include lesionectomies, focal resection involving an ictal onset zone, multiple subpial transection (MST: a series of parallel transections in the cortical gray matter identified by EEG as the ictal onset zone), corpus callosotomy (transection of a portion of the corpus callosum connecting the two hemispheres), and anatomical or functional hemispherectomy [63]. Anatomical hemispherectomy consists of removal of cortical and subcortical tissue in an entire hemisphere, sparing brainstem structures. Functional hemispherectomies have largely replaced anatomical hemispherectomies due to decreased risk of hemorrhage and hydrocephalus. A functional hemispherectomy consists of removal of the temporal lobe, corpus callosotomy, and disconnection of the frontal and occipital lobes. In many cases, two or more procedures are combined, e.g., focal resection with corpus callosotomy or MST.

Mechanisms(s) of Action

The mechanisms of action of neurosurgical interventions in controlling status epilepticus include disruption of the epileptogenic network(s) through either resection of the epileptic focus with lesionectomies, hemispherectomies, and other focal resections; disruption of contralateral spread of seizure activity with corpus callosotomy; or disruption of focal spread of seizure activity in the case of multiple subpial transection (see Table 18.1).

Treatment Algorithms/Techniques

A variety of surgical techniques has been employed (see Table 18.2). The seizure focus can at times be identifiable based on structural findings on MRI or CT of the brain; scalp or intracranial electroencephalography (EEG) or both; interictal flurodeoxyglucose (FDG) positron emission tomography (PET); ictal single photon emission computed tomography (SPECT); or a combination of these tests. If a single focus is identified, focal resection is likely to yield the greatest probability of seizure control. If the seizure focus is located within eloquent cortex (areas critical for function such as Broca's or Wernicke's area or the primary motor cortex), multiple subpial transection may be less likely to cause a functional deficit, while still disrupting the epileptogenic network. Callosotomy is designed to disconnect the two hemispheres and prevent contralateral spread of seizure activity.

Evidence for Efficacy

A 2012 review [3] of studies reporting resective neurosurgery as a form of treatment for status epilepticus identified 36 cases reported among 15 studies and of these cases, status epilepticus stopped following surgery in 33 (92%). In a recent retrospective study of 15 children treated for refractory status with surgical intervention guided by intraoperative electrophysiological evaluation, ictal SPECT and FDG PET, status epilepticus resolved in all cases [64] (see Table 18.3).

Contraindications, Side Effects, and Other Considerations

All surgical interventions carry the risk of hemorrhage, infection, pain, and adverse reaction to anesthesia including death (see Table 18.4). Focal cortical resections and MST carry the risk of functional deficits such as hemiparesis and aphasia depending upon the location of the resection. Corpus callosotomy carries the risk of disconnection syndromes including unilateral apraxia, tactile anomia, and pure word blindness [65].

Ketogenic Diet Therapies

Background

In 1921, R.M. Wilder published the first article describing a ketogenic diet as a potential treatment for epilepsy [66]. Ketogenic diets are designed to mimic the fasting state while maintaining adequate nutrition, resulting in the metabolism of fat and production of ketone bodies. The "Classic Ketogenic Diet" (CKD) is composed of 90% of intake of fat calories and 10% of protein and carbohydrates combined. In recent decades, modifications have been made to the CKD to attempt to improve compliance by allowing for higher carbohydrate intake with diets such as the Modified Atkins diet (MAD) and the low glycemic index treatment (LGIT). The CKD is available in a formula and can therefore be administered to a patient in refractory or super-refractory status epilepticus via feeding tube, while MAD and LGIT require the ability to take nutrition orally.

The ketogenic diet has been shown to be effective in several animal models of status epilepticus and has been used in treating refractory and super-refractory status epilepticus in humans over the past several years.

Mechanisms(s) of Action

Studies of animal models of status epilepticus have shown multiple potential mechanisms of action of the ketogenic diet in treating seizures and status epilepticus (see Table 18.1). Ketone bodies such as betahydroxybutyrate, acetoacetate, and acetone have both GABAergic and glutamatergic effects [67]. One study showed that the ketogenic diet produced an increase in activation of adenosine A1 receptors [68]; another hypothesized that the ketogenic diet alters glycolysis and activates potassium ATP channels [69]; and a third study suggested that the diet inhibits the mammalian target of rapamycin (mTOR) pathway [70]. Several studies have suggested that ketogenic diets have anti-inflammatory properties [71–74].

Treatment Algorithms

Several treatment algorithms have been proposed for managing status epilepticus with a ketogenic diet (see Table 18.2). A 4:1 ratio (of fat to carbohydrates and protein combined, in grams) CKD has been used most frequently, but some studies have used a 3:1 ratio diet [75]. One study described use of the MAD in treating nonconvulsive status epilepticus in two children [76], and another described a patient with status epilepticus caused by a mutation of the mitochondrial polymerase gamma, successfully treated with the LGIT [77]. Whether or not patients fast prior to initiating the diet, fasting duration, and the duration during which patients are advanced to full calories, vary from one study to the next. Given that patients with status epilepticus are often intubated and receiving enteral nutrition at the time the diet is initiated, it is most often introduced by enteral formula. Recent studies, however, have also demonstrated safety and feasibility of an intravenous ketogenic diet for children [78] and adults [79] with super-refractory status epilepticus.

Evidence for Efficacy

A review of published case reports and case series of patients treated for status epilepticus with ketogenic diets was published in 2013 and at that time, 10 studies described outcomes in 32 patients [80]. Since then, four additional studies have been published [75, 81–83]. Overall, 14 published case reports and case series have described treatment of status epilepticus with a ketogenic diet in 52 patients (37 children

and 15 adults). Status epilepticus resolved in 44 of those 52 patients (85%), but continued intermittent seizures following status epilepticus cessation were reported often with long-term follow up (see Table 18.3).

Contraindications, Side Effects, and Other Considerations

Ketogenic diets are contraindicated in patients with certain metabolic disorders that affect carnitine metabolism, and in beta-oxidation defects, pyruvate carboxylase deficiency, porphyria, acute pancreatitis, and hepatic failure, in which high-fat or low-carbohydrate intake can exacerbate the underlying condition [84]. Teratogenic effects of ketogenic diets are unknown, so these treatments are avoided in pregnancy. Finally, one study reported a fatal propofol infusion syndrome in the setting of ketogenic diet administration [85], so co-administration is usually avoided [86]. The most common short-term side effects include constipation, nausea, vomiting, and elevated fasting lipids (see Table 18.4).

Conclusions

Evidence is building to support the use of nonpharmacologic interventions for the treatment of refractory and super-refractory status epilepticus such as TH, neurostimulation, neurosurgical interventions, and ketogenic diet therapies. Combining these therapies with one another and with various anesthetic drugs may have a potential synergistic effect in halting status epilepticus [8, 10, 20]. Large-scale prospective, double-blinded, randomized clinical trials are necessary to determine the safety, feasibility, and efficacy of these treatments and when in the overall treatment algorithm for status epilepticus each is appropriate to introduce.

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Part III
Nonconvulsive Status Epilepticus

Evolving Concepts of Nonconvulsive Status Epilepticus

19

Frank W. Drislane

The Early History

Although convulsive status epilepticus was very likely observed millenia ago, as noted by Kaplan and Trinka in Chap. 1, "History of Status Epilepticus," nonconvulsive status epilepticus (NCSE) is a much more recent concept. Most nonconvulsive seizures or NCSE are manifested as episodes of diminished responsiveness or unusual behavior —probably considered as caused by supernatural forces until the most recent centuries [1]. Perhaps by association with other forms of epilepsy with altered consciousness, from behavior at the beginning of seizures or in a postictal state, or occurring just before or after convulsive status, some speculation about the possible existence of NCSE explaining such episodes emerged by the 1800s.

By the late 1800s, Charcot and others had described cases suggestive of NCSE. In his "Leçons du Mardi" at the Salpêtrière, he interviewed and discussed a patient who wandered the streets of Paris without memory of the wanderings [2]. Charcot concluded that this state of apparent somnambulism derived from a nonconvulsive form of prolonged ongoing seizures. In a similar vein, Clark and Prout described many spells of strange behavior in their reviews of status epilepticus (SE) [3].

Nevertheless, without an appreciation of the role of electricity in the nervous system (starting to emerge in the seventeenth and eighteenth centuries [4]), it would be hard to conceive of a modern understanding of NCSE. Clinical descriptions of confusional states, even with twitching of facial or limb muscles, and even in patients with epilepsy, were insufficient to prove that NCSE was a proper diagnosis.

A more sophisticated understanding of NCSE awaited Berger's invention and development of the electroencephalogram (EEG) in the 1920s, making it possible to record the previously suspected electrical activity of the brain [5]. Berger began correlating EEG activity, as a measure of brain electrical function, with psychologic and behavioral abnormalities and eventually, epileptic seizures [6]. Only then could the strong neurophysiologic relationship between convulsions and these nonconvulsive episodes become more evident. Such clinical-EEG correlations showed beyond doubt that NCSE was part of epilepsy, and not due to psychiatric or nonepileptic fugue states.

Classic Absence Status Epilepticus and Complex Partial Status Epilepticus

Over the next few decades, the "classical" NCSE syndromes were described. Although *petit mal intellectual* had been postulated in the nineteenth century, Lennox observed that altered mental status could be caused by nonconvulsive seizures and found that a series of individual absence seizures with characteristic EEG discharges could persist for much longer than was generally recognized [7]. In 1945, he described the clinical and EEG features of absence status in his cousin and coined the term *petit mal status* (see Chap. 1) [8]. In 1954, Penfield and Jasper described simple partial status epilepticus or *aura continua* in the form of recurrent epileptic sensory phenomena [9].

Complex partial status epilepticus (CPSE) was not as easy to verify by EEG, and its first thorough description was in 1956, when Gastaut and Roger described a nurse whose seizures may have lasted months [10]. In the 1970s and 1980s, CPSE was the subject of isolated case reports [11, 12]. It was considered rare, and by 1985 only 17 clearly identified cases had been published [13]. Eventually, CPSE (or more recently, "focal SE with impaired consciousness") was recognized as far more common than absence SE [14, 15].

F.W. Drislane (✉)
Department of Neurology, Harvard Medical School, Beth Israel Deaconess Medical Center, KS 457, 330 Brookline Ave, Boston, MA 02215, USA
e-mail: fdrislan@bidmc.harvard.edu

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Proliferation of NCSE Varieties

In its classic appearance, absence SE occurs in patients with earlier absence epilepsy or other idiopathic generalized epilepsies (IGEs) [16–18] (see Chap. 15, "Status Epilepticus in the Idiopathic Generalized Epilepsies"). In the 1970s to 1990s, there were several new examples of generalized NCSE related to the IGEs [18]—but not all identical to absence SE. There were also many new examples of focal-onset NCSE, but some occurred without the impaired consciousness characteristic of CPSE, thus not truly examples of CPSE. Many involved focal cognitive deficits or behavioral abnormalities difficult to distinguish from the manifestations of other focal brain lesions such as strokes or tumors. Examples include "ictal" aphasia, hemianopia, dysmnesia (without diminished awareness), agraphia, psychosis, and neglect syndromes (see Chap. 21, "Cognitive Manifestations of Focal Status Epilepticus")—but all with maintained alertness and awareness, thus focal NCSE but not truly CPSE. Many of the episodes of generalized and focal NCSE were exacerbations or prolongations of the patient's earlier epileptic seizures of the same type.

Despite recognition of these many different forms of NCSE, even into the 1990s descriptions and classifications of NCSE generally tended to divide NCSE into two types: "absence SE" and CPSE. The former included all NCSE with generalized spike and slow wave discharges on the EEG. "CPSE" (even without the typical altered consciousness) was the label for SE with focal discharges on the EEG or a clear focal-onset clinically and was considered the equivalent of prolonged or repetitive complex partial (or at least focal-onset) seizures [19]. With all the varied forms of generalized and focal NCSE discovered by then, however, this simplified dichotomy for types of NCSE was no longer tenable.

Further, generalized NCSE could not always be separated easily into primary generalized SE or focal-onset forms spreading to a broader or generalized distribution. Secondarily generalized NCSE was the true diagnosis in many reports of NCSE described then as "absence SE," but it had little to do with typical absence epilepsy. Often, generalized NCSE in adults without prior IGE or other epilepsy syndromes was not truly "absence" SE but secondarily generalized from a focus [20, 21], though the EEG and clinical signs might be generalized at the time of diagnosis. Many were precipitated by metabolic derangements. Seizures might appear similar clinically (and on EEG) to cases of primary generalized NCSE, and it could be impossible to tell the difference at the time of presentation. True absence SE, e.g., in the IGE syndromes, is relatively uncommon, typically easy to treat, and has an excellent prognosis. Secondarily generalized NCSE usually has underlying (and sometimes severe) lesions, is much harder to treat, and carries the prognosis of the underlying illness.

Boundary Syndromes

Over the past few decades, many epileptologists have written, appropriately, of the "ictal–interictal continuum," but even in the mid-twentieth century, it was clear that there were many syndromes that could not be determined with certainty as being either epileptic or nonepileptic, although they were clearly associated with clinical deficits or abnormal behavior somehow related to epilepsy. Such "boundary syndromes" [22] do not fit easily into categories of SE (or *not* SE). Many are syndromes with markedly abnormal baseline neurologic conditions and epileptiform abnormalities on EEG in which it is difficult or impossible to determine what role the epileptiform discharges have in causation of the clinical manifestations. Many or most are pediatric syndromes that occur within a broad range of illnesses such as the Lennox–Gastaut syndrome (LGS). Many of the EEG patterns raise the possibility of epileptic seizures without confirming them. Among the best examples are Electrical Status Epilepticus in Sleep and Atypical Absence Status Epilepticus.

Electrical Status Epilepticus in Sleep (ESES)

Several of the most prominent pediatric epilepsy syndromes associated with underlying developmental delay or regression demonstrate activation of epileptiform abnormalities during sleep (see Chap. 27, "Pediatric Status Epilepticus"). ESES implies activation by sleep of persistent epileptiform activity suggestive of SE—but not all children with these EEG findings have clinical seizures. Some have an associated *clinical ESES* syndrome, with ESES on the EEG along with progressive cognitive decline. A related "epileptic encephalopathy" is continuous spikes and waves during slow sleep (CSWS), a pediatric epilepsy syndrome in which continuous generalized (if sometimes asymmetric) spike-and-wave complexes at 1.5–3.5 Hz occur during at least 85% of slow wave sleep [23]. CSWS usually begins in the first decade of life in children who were neurologically normal before the onset of generalized convulsions or atypical absence and atonic seizures [24]. Most of these children have seizures, global behavioral problems, and regression of cognitive function. Usually the EEG "quiets" eventually, and most seizures resolve, but cognitive and behavioral problems persist [23, 24]. It is difficult or impossible to know if the epileptiform discharges are responsible for (i.e., cause) the clinical deficit, or if both the

discharges and clinical deficits are manifestations of the same underlying brain illness.

In the related Landau–Kleffner syndrome (LKS), children present with an acquired aphasia, seizures, and a behavioral disorder despite previously normal language development [25]; some start with a gradual deterioration in language comprehension and speech output, with apparent word deafness or a form of auditory agnosia [26]. LKS is often treated with ASDs, especially benzodiazepines (BZDs), with a goal of eliminating epileptiform discharges in the hope that the epileptic process contributes to the cognitive deterioration—for which there is now some evidence (see Chap. 27).

Atypical Absence Status Epilepticus

Atypical absence status epilepticus (AASE) is relatively rare. It is definitely a form of NCSE but also an illness in which it is difficult to be sure when the NCSE starts and stops, and how to distinguish the SE from a baseline dysfunction. It often occurs within LGS, with substantial neurologic deficits, developmental delay, and severe encephalopathies [27]. Patients may have nonconvulsive and additional tonic, atonic, and myoclonic seizures.

Clinical manifestations often include a further slowing or reduction in cognitive function—from a poor baseline. AASE can go on for days, with an apparently gradual onset and termination [28]. AASE is more complicated than typical absence SE and includes a significant background encephalopathy, both clinically and on EEG [27]. As with typical absence SE, the EEG shows rhythmic generalized spike and polyspike and slow wave discharges, but with a slower (usually ~2.5 Hz) frequency ("slow-spike-and-wave") and somewhat less rhythmicity and less perfect symmetry than in absence seizures [28]. Often, there are no overt clinical seizures, and it can be very difficult to differentiate AASE from the patient's encephalopathic, developmental, or psychiatric behavioral baseline. Electrographic seizures may not correlate well with clinical manifestations. As with absence SE, seizures may exhibit exacerbation with ASDs such as carbamazepine and amelioration with ethosuximide and BZDs [29]. Intravenous BZDs may interrupt the EEG discharges without changing behavior substantially, and it is unclear what role the epileptiform discharges play in the clinical syndrome, i.e., it is another "boundary syndrome."

Triphasic Waves

The significance of triphasic waves (TWs) has also been perplexing ever since their early description by Bickford and Butt [30]. TWs are moderate to high voltage (100–300 μV) rhythmic complexes, often recurring at 1–2 Hz, frequently in clusters, but sometimes recurring continuously at 0.5–2 Hz, often associated with diminished levels of consciousness [31]. TWs are commonly state-responsive, increasing with stimulation, and attenuating with deeper stupor or coma, and may be abolished or regress after administration of IV ASDs or other drugs [31]. TWs can have an "epileptiform" shape; when they are rapid and rhythmic, it can be hard to determine whether they represent seizure activity, an encephalopathy, or both [32–34]. Most do not appear to signify ongoing seizures, but some are very sharp and rhythmic and may appear identical to the discharges that occur in definite NCSE, especially when their frequency exceeds 1.5 or 2 Hz [35].

Features of TWs that may help to distinguish encephalopathic manifestations from epileptic phenomena are in Table 19.1 [32]. Greater frequency, rhythmicity, and sharpness of TWs, with polyspike components may well indicate an epileptic process, while an anteroposterior gradient and blunter TWs without rhythmicity suggest an encephalopathy. Resolution of TWs in response to administration of BZDs might suggest a diagnosis of NCSE, but BZDs may also abolish typical, even rhythmic, TWs from an underlying encephalopathy, usually without clinical improvement [31]. Still, some true NCSE also does not respond to ASDs or may give way to an encephalopathic pattern without clinical improvement. In the end, whether a particular morphology or evolution represents an encephalopathy or NCSE must be determined by an experienced electroencephalographer—not neglecting clinical data.

The Continuous EEG Monitoring Era and "Non-classic" Nonconvulsive Status Epilepticus

Just as Berger's development of the EEG facilitated the discovery and description of the classic forms of NCSE, a new burst of discovery was prompted by another technologic innovation, continuous EEG (C-EEG) monitoring, especially when carried out on critically ill patients in intensive care units. With routine or moderately prolonged EEGs, Fagan, Towne, DeLorenzo, and their colleagues [36–38] found NCSE in many critically ill patients, especially in comatose patients and after GCSE. Soon thereafter, with C-EEG monitoring of critically ill patients, Hirsch and colleagues found that, in several selected groups of patients, about 20% were having nonconvulsive seizures or NCSE [39–41], especially when they had co–occurrence of complicated medical illnesses, earlier epileptic seizures, or both.

The forms of NCSE discussed earlier, both focal and generalized, constitute the "classic" types of NCSE—

Table 19.1 Triphasic waves versus periodic epileptiform discharges

Triphasic waves:
Surface-negative, blunted triphasic complexes with: (a) low-amplitude, blunted, negative first phase (often wide-based); (b) dominant, steep positive second phase; and (c) slow rising third "slow-wave" component. No polyspike components
Complex duration: 400–600 ms
Amplitude: 100–300 μV on referential montage; smaller on bipolar
Frequency: 1.0–2.5 Hz (typically 1.8 Hz)
Persistence: wax and wane, but >10% of a standard 20 min recording
Evolution/reactivity: decrease with sleep, drowsiness, or after benzodiazepines; increase and reappear with arousal or noxious stimulation
May exhibit phase-lag, seen best on referential montage
Periodic epileptiform discharges:
Surface-negative bi-, tri-, or polyphasic discharges with spike, sharp, polyspike components, or slow wave complexes, or combinations of these
Complex duration: 60–600 ms (mean 200 ms)
Amplitude: 50–300 μV (usually up to 150 μV)
Frequency: 0.2–3 Hz (usually 0.5–2.0 Hz)
Persistence: minimum of 10 min in an EEG recording
Evolution: static—with only minor variability in the above characteristics

Adapted from Boulanger and colleagues[32]

absence SE and similar generalized forms of NCSE on the one hand, and CPSE or focal-onset NCSE with dyscognitive features or altered awareness on the other. Most or many cases are related to (and often exacerbations of) prior epilepsy syndromes, sometimes with an acute precipitant. Over the last two decades, however, large and increasing numbers of cases of NCSE are not of these "classic" types but are rather related to acute and serious medical, neurologic, or traumatic illnesses—occasionally superimposed upon epilepsy syndromes but more often arising anew during an acute illness. Often, those other illnesses contribute to the reduced level of responsiveness and, in turn, retard the recognition of NCSE and rendering its clinical significance harder to determine. Consequently, the diagnosis rests heavily on the electroencephalography (EEG), which often shows rapid and rhythmic epileptiform discharges in the absence of clinical signs of seizures. These "non-classic" cases are the most common types of NCSE in ICUs today.

Old diagnostic quandaries persist but are now augmented by the EEG patterns found with high and increasing frequency by C-EEG monitoring. Even while the old "borderline syndromes" remain common clinical problems, periodic discharges (both focal and generalized) are probably the most rapidly growing area of boundary syndromes. They occur often in patients with diminished alertness or other neurologic dysfunction, but with a large variety of EEG findings. Periodic discharges and neonatal seizures are large "growth areas" of boundary conditions in the age of C-EEG monitoring.

Periodic (Epileptiform) Discharges

The significance of sharp (potentially "epileptiform") and rhythmic EEG features varies remarkably and ranges from the "irritative" (post-, inter-, or pre-ictal) to the "actively seizing"—along an "ictal-interictal continuum" [42, 43]. Periodic discharges include: periodic lateralized (epileptiform) discharges, traditionally labeled PLEDs, and more recently, LPDs; bilateral independent periodic lateralized (epileptiform) discharges (BiPLEDs, or BIPDs); and generalized periodic (epileptiform) discharges (GPEDs, or GPDs). For a comprehensive review of periodic discharges, see Chap. 5, "Periodic EEG Patterns."

Periodic Lateralized (Epileptiform) Discharges

From the time of their initial report by Chatrian and colleagues [44], periodic lateralized epileptiform discharges have been controversial, but this only intensified as technology improved. They consist of spike, sharp, or polyspike components, with variable following slow wave complexes, usually recurring at 0.5–2 Hz, distributed broadly over most of one hemisphere. Between discharges, the background activity is usually attenuated and slow. Over time, the discharge frequency may decline, and most PLEDs resolve within weeks [44].

PLEDs, or LPDs, occur most commonly after acute large structural lesions such as strokes (the most common cause),

tumor, or infection, but also in chronic seizure disorders and static lesions [45, 46]. Patients with PLEDs are often obtunded, with focal neurologic deficits and often, focal motor seizures; *epilepsia partialis continua* (EPC) is common. Clinical seizures occur in at least 80% of patients with PLEDs and electrographic seizures in even higher proportions; many have had prior SE [46]. Half of patients without prior epilepsy who survive the acute illness develop long-term epilepsy [47].

Most EEG-ers do not consider PLEDs to be a manifestation of ongoing seizures or SE, at least at the time of the recording [47, 48]; they are often considered "the terminal phase of status epilepticus" [46]. Nevertheless, they are highly associated with clinical seizures [46]. Patients with "PLEDs plus," or LPDs+ (with lower voltage rhythmic epileptiform discharges, or other rhythmic patterns between the higher voltage periodic sharp waves) are more likely to have clinically evident epileptic seizures [49].

Periodic discharges are often considered "ictal" (the sign of an ongoing seizure) if they occur consistently with stereotyped clinical behavior that appears epileptic. More rapid discharges (at least 2 Hz) would also be interpreted as representing seizures (and if prolonged enough, SE) by most EEG-ers. PLEDs are also likely to be "ictal" if the EEG discharges resolve and clinical symptoms improve after ASD treatment. Some studies have found focal hyperperfusion on SPECT scans [50, 51] or evidence of focally increased metabolic activity on PET scans at the time of PLEDs [52], suggesting that PLEDs are the sign of ongoing seizures. Sometimes, PLEDs are definitely seizures, even with no structural lesions and EEG discharge intervals as long as 4 s [53], as shown by resolution of clinical deficits along with slowing of the discharges, spontaneously or in response to BZDs. PLEDs observed during EPC are certainly a manifestation of seizures [54].

Generalized Periodic (Epileptiform) Discharges

Generalized periodic (epileptiform) discharges are continuous generalized spikes, polyspikes, sharp-and-slow waves, or sharp waves, often with a repetition rate >1 Hz, typically arising from a diffusely slow or low voltage background [55]. They are a common finding in C-EEG monitoring in the ICU and highly associated with an abnormal mental status, coma, convulsions, NCSE, and a poor outcome [56] (see Chap. 5). Many are seen following anoxia or other catastrophes, metabolic insults, recent overt seizures, or in the late stages of GCSE [57]. They are highly associated with clinical seizures but not necessarily indicative of ongoing seizures at the time [58, 59]. Some consider most GPDs to be seizures and recommend aggressive ASD therapy [57], while others believe that they are the sign of neuronal injury but not actual seizures and not requiring aggressive treatment; this may depend in large part on the frequency of the GPDs. One study did not find any features that could distinguish clearly between GPDs after anoxia and GPDs after SE [60], even though those conditions have markedly different implications for prognosis and treatment. GPDs tend to persist even with aggressive therapy, and it is not known whether patients benefit from ASD treatment for them.

Some periodic discharges appear to fluctuate and can lie on either side of the "borderline." Focal or generalized periodic and quasi-periodic discharges can also be elicited in stuporous or comatose patients upon stimulation —"stimulus-induced rhythmic, periodic, or ictal discharges" or SIRPIDs, which usually abate after the stimulus recedes [61]. Hirsch has demonstrated persuasively that some SIRPIDs should be considered a sign of arousal and that others (with clear clinical manifestations) are definite seizures [62].

Neonatal Seizures and Status

Another area in which C-EEG monitoring has played an increasingly large role in trying to determine whether a patient is having active seizures is that of neonatal seizures and NCSE—also discovered recently to be much more common than previously suspected [63]. During seizures and NCSE, neonates may exhibit minimal or no change from their clinical baselines [64]. NCSE can remain underdiagnosed if EEG monitoring is not utilized, especially in neonates with severe brain injury [65]. Also, electrographic patterns of neonatal seizures differ from those in older patients, often remaining localized to smaller areas. Some show evolution in frequency, amplitude, morphology, or spatial distribution, but many do not [65]. Many neonatal seizures last 2–3 min but recur frequently; prolonged continuous seizures are less frequent than in adults [66]. Given the clinical subtleties of neonatal seizures and NCSE, clinicians are increasingly dependent on C-EEG monitoring, but with many of the same uncertainties and problems encountered in critically ill adults with markedly abnormal EEGs. Often, it is difficult or impossible to determine if the electrographic abnormalities or epileptiform discharges cause the clinical deficits.

ACNS Criteria

To assist in dealing with these complex but important electroclinical quandaries, Hirsch and colleagues, working in a subcommittee of the American Clinical Neurophysiology Society (ACNS), proposed standardized terminology for EEG patterns [67] and criteria for diagnosing seizures on

Table 19.2 American Clinical Neurophysiology Society research criteria for nonconvulsive seizures (and, if >30 min, nonconvulsive status epilepticus)

(1) Repetitive generalized or focal spikes, polyspikes, sharp waves, spike-and-wave or sharp-and-slow wave complexes, or other rhythmic waveforms at >2.5/sec, lasting longer than 10 s
(2) The same waveforms as above, with discharges <2.5/sec, but with …
(a) clear clinical ictal phenomena, such as facial twitching, nystagmus, or limb myoclonus, or
(b) an unequivocal evolution of the rhythmic pattern, including increase or decrease in frequency (by >1 Hz), change in discharge morphology, or in location (gradual spread of rhythmic activity into or out of a region involving at least 2 electrodes). Changes in discharge amplitude or "sharpness" alone are not sufficient, or
(c) rhythmic theta or delta waves at >1/sec, with the additional criterion of an unequivocal clinical improvement, or improvement on EEG (such as resolution of epileptiform discharges and reappearance of previously-absent normal background rhythms and reactivity) or both, following quickly after acute administration of rapidly acting ASDs, typically benzodiazepines (Resolution of discharges leaving a slow background alone, without clinical improvement, would not suffice.)

Adapted from Chong and Hirsch [43] and Young and colleagues [68]

electrographic (EEG) grounds, attempting to discern which periodic discharge patterns are likely to be "ictal," i.e., indicative of ongoing epileptic seizures (summarized most concisely by Chong and Hirsch [43] and detailed in several papers [68–70]). Periodic discharges indicating definite seizure activity are rapid (>2.5 Hz) or show clear evolution, like the EEG patterns of typical seizures. Straightforward examples of NCSE on EEG conform to "ACNS criteria" and continue for over 30 min (Table 19.2).

The range of different EEG patterns in clinically diagnosed NCSE, however, is extensive [70]. EEG waveform morphologies include rhythmic slowing, sharp waves, spikes, and mixtures of these features [71]. Discharges may be continuous, persistent with brief pauses of a few seconds, or intermittent. Many EEGs are more ambiguous, with slower, more blunted waveforms, sometimes resembling TWs [32]. Over time, NCSE patterns tend to evolve in morphology, voltage, and frequency, and wax or wane. This EEG-based diagnosis should be made in a patient with a neurologic deficit (due to seizure activity) that has not resolved or returned to clinical baseline [43].

The ACNS criteria or guidelines have been of great value in standardizing diagnosis for clinical studies, and their use has facilitated valuable studies of critically ill patients, many of whom have, or are suspected of having, the "non-classic" forms of NCSE. Their use by consortia has enabled valuable multicenter studies [56, 72].

Problems with the Criteria

While the ACNS criteria have facilitated studies that have improved understanding of nonconvulsive seizures and NCSE, they do not always determine a clear diagnosis for an individual patient. The criteria have good *specificity* for nonconvulsive seizures and NCSE and offer greater certainty in their diagnoses. They are often used clinically but were designed primarily as guides for research purposes (thus the need for specificity), but their lack of *sensitivity* can be a problem, given the wide range of potential findings in patients with (subsequently) clinically confirmed NCSE [70, 71]. There are patients whose EEGs do not meet these criteria who are very likely having seizures or NCSE [71, 73], so clinical judgment remains crucial in diagnosis.

Sometimes, seizures and NCSE are readily apparent on the EEG, with characteristic or even "classic" features. Similar EEG findings, however, can be seen in metabolic and other encephalopathies, and many EEG patterns are neither pathognomonic nor easy to interpret.

Even determining focal versus generalized NCSE patterns can be difficult. During NCSE, the EEG may show epileptiform discharges generalized at the onset; discharges that begin focally, with or without secondary generalization; or both focal and generalized abnormalities [74]. Among pediatric ICU patients, focal or multifocal NCSE (65%) was more common than generalized SE (35%) [63].

Although EEG is the most reliable diagnostic test for nonconvulsive seizures and NCSE, it is not always conclusive. As noted in the ACNS recommendations, a response to treatment (an "ASD challenge") can be helpful. Some patients with less "classic" EEG findings show a clinical and electrographic response to BZDs or other ASDs, and in the appropriate setting, a rapid response can be diagnostic of NCSE. Lorazepam or another ASD may be given in small sequential doses, while monitoring blood pressure, respiration, and oxygenation. To be diagnostic of ongoing seizure activity, there should be prompt resolution of epileptiform features on the EEG and clear improvement in the patient's clinical state, or complete cessation of electrographic seizure activity with return of a normal EEG background [75]. Intravenous BZDs may abolish electrographic seizures, but they can also suppress nonepileptic EEG patterns such as TWs [31], so electrographic improvement alone does not prove that a particular EEG pattern was a seizure. The diagnosis must be made taking into account both the clinical context and the EEG findings.

Importantly, lack of prompt improvement with ASDs does not refute a diagnosis of NCSE. Frequently, the response to ASDs is very delayed or inconclusive [36, 75], even in patients with definite NCSE. A rapid clinical response is uncommon, especially in obtunded or comatose patients [76], and sedation from a BZD may also impair a clinical response. When the ASD challenge "works" a diagnosis is made; when not (probably more common) it does not disprove the presence of NCSE.

The Special Case

Probably, the most important "non-classic" NCSE clinically is the continuation of SE after unsuccessful (and often inadequate) treatment of generalized convulsions or GCSE, a relatively common finding on C-EEG monitoring. The EEG may show rapid epileptiform discharges following the apparent control of GCSE, without clinical signs of persistent seizures. In this subtle form, the epileptiform seizure discharges continue on the EEG and the patient remains unresponsive, even while the motor manifestations (convulsions) have ceased. In this setting, a wider range of potentially epileptiform EEG patterns should be considered as indicative of ongoing NCSE. Most epileptologists agree that when these EEG changes are marked, this NCSE should be considered a later stage of GCSE in terms of its pathophysiology and clinical implications and should be treated expeditiously.

ACNS criteria make a diagnosis of NCSE when there are "subtle" motor signs such as blinking or myoclonus. Logically, if patients with these EEG patterns following generalized seizures and GCSE are considered in NCSE when they have clear "subtle signs," patients with the same EEG patterns in the same setting, even without clinical signs, should probably be diagnosed the same.

These patients with minimal or no motor signs have been said to be in "subtle generalized convulsive" SE [57]. The EEG may show discontinuous epileptiform activity with brief bursts of generalized spikes or GPDs [57, 77]. Some consider these EEG patterns to indicate ongoing SE only if the patient had previous clinical seizures or SE [78]. These patients have high morbidity and mortality [57, 68, 78, 79; see also Chap. 5]; and most agree that the urgency of treatment continues with the persistent electrographic seizures, especially when preceded by generalized convulsions —even while acknowledging that abolition of electrographic seizures does not always lead to clinical improvement.

There are also many other patients with ongoing electrographic seizure activity (whether following GCSE or not), with severe medical illnesses such as cerebrovascular disease, sepsis, or marked metabolic derangements. There is often substantial uncertainty in determining whether the EEG pattern represents seizure activity or not [43]. ACNS criteria help, but they are not always sensitive enough in actual clinical cases. In clinical practice, rhythmic, relatively rapid (>2 Hz) epileptiform discharges, typical for SE on the EEG, without obvious clinical manifestations, should usually be considered SE rather than simply an encephalopathy with epileptiform discharges—even when treatment does not effect a clinical improvement. The EEGs are very similar to those in published NCSE studies [74]; these patterns predict clinically evident seizures when seen on emergence from highly sedating therapy for refractory SE [80, 81]; and some patients with these EEGs respond well to ASDs [82]. How aggressively to treat, however, remains very controversial (see below).

This prolonged electrographic (nonconvulsive, often secondarily generalized, "non-classic") seizure activity is very common in critically ill patients. In analyzing the correlations of these EEG patterns and corresponding neurologic deficits, many terms have been used. Some are referred to as in "subtle GCSE," as above [57], and some in electrographic status epilepticus (ESE) [77]. Others refer to "nonconvulsive status epilepticus in coma," but not all patients with ongoing electrographic seizures are comatose. Some label these patients with severe medical illnesses as having "epileptic encephalopathies," indicating that the underlying disease causing the discharges is key, and that the epileptic component is not primary and may not respond to ASDs. This term, however, is probably best reserved for childhood conditions such as those associated with ESES (above).

The Status of Nonconvulsive Status Epilepticus in 2017

The Nature of Nonconvulsive Status Epilepticus—Definition

In 2017, there is a much greater appreciation than before of the subtleties and complexities of NCSE, but it can still be difficult to formulate a precise definition, in part because its clinical manifestations are protean and its pathophysiologic implications uncertain. Also, EEG findings, while crucial for diagnosis, are often ambiguous or controversial, and the response to ASDs may be subtle.

What is a seizure? The most recent ILAE definition of an epileptic seizure is "a transient occurrence of signs and/or symptoms due to an abnormal excessive or synchronous neuronal activity in the brain [83]." More briefly, this could be a transient "neurologic clinical deficit due to abnormal, usually hypersynchronous, electrical brain activity."

What then is nonconvulsive status epilepticus? Gastaut stated that SE was a continuation of one of the many

different types of epileptic seizures [84], but it has become clear that SE is, to a large extent, a different pathophysiologic process than is seen in individual seizures—with "a failure of …. seizure termination or …. initiation of mechanisms [leading] to abnormally prolonged seizures" [85], and with manifestations different from those of individual seizures.

A definition of NCSE should include three elements: that there is a clinical abnormality in neurologic function (other than convulsions); that there is persuasive evidence that the dysfunction is due to an epileptic process, i.e., seizure activity; and that it is abnormally prolonged. Briefly, NCSE is "a state of prolonged seizure activity with a resultant change in behavior or level of consciousness [22]."

The ILAE 2015 Task force definition stated: "Status epilepticus is a condition resulting either from the failure of the mechanisms responsible for seizure termination or from the initiation of mechanisms, which lead to abnormally prolonged seizures (after time point t1). It is a condition, that can have long-term consequences (after time point t2), including neuronal death, neuronal injury, and alteration of neuronal networks, depending on the type and duration of seizures [85]." This definition provides pathophysiologic insight and illustrates starkly the difference between individual seizures and SE. It also provides a clear impetus for prompt treatment, though it does not specify the exact nature of NCSE, or what it *is*.

The Clinical Deficit

The clinical deficit typically encompasses an (epileptic) impairment of mental status, cognition, or behavior. During the proliferation of reports of different forms of NCSE a few decades ago, clinical manifestations were recognized as broader and more protean, making it difficult to say exactly what clinical changes should be expected. Beyond a change in alertness or behavior, there may also be a change in sensory perception (e.g., auditory, visual, somatosensory, or psychic) or aphasia, dysmnesia, neglect, alexia, etc. [86]; see also Chap. 21.

Evidence that the Deficit Is Due to Epileptic Seizure Activity

Because NCSE is considered an epileptic process without convulsions (or no more than minimal motor manifestations), but with pleomorphic clinical abnormalities, almost all diagnostic criteria insist on EEG evidence of continuing or very frequent epileptiform activity, corresponding closely, or somewhat, to the ACNS criteria. There are also other diagnostic tests to show that a patient is in NCSE, including some imaging techniques (almost always far less convenient and less commonly used) [87, 88] and the "ASD challenge" (described above)—with its own limitations.

Still, controversy persists regarding which EEG patterns are diagnostic of, or consistent with, NCSE, and there are no absolute (or at least, widely agreed upon) criteria for the diagnosis of ongoing seizures by EEG. The determination of whether a particular EEG pattern represents an encephalopathy or NCSE (or both or neither) relies on the determination that certain patterns are "ictal" in nature, i.e., signifying ongoing epileptic seizures. Some EEG findings are persuasive on their own, but in other cases identical EEG findings may indicate ongoing seizures in one patient and not in another—or at least not seizures that a wise neurologist would treat.

In clinical practice, neurologists cannot be restricted to diagnosing NCSE by ACNS criteria alone, helpful as they are, especially in clinical studies. It is not sufficient to report to the requesting physician that the EEG "lies somewhere on the continuum" (the ictal-interictal continuum) or that ASDs are unwarranted because any putative electrographic seizure activity "did not meet ACNS criteria"—especially in the "special case" of possible NCSE after insufficient treatment of GCSE. For a clinical decision on treatment or management, the likelihood of NCSE must be determined by an experienced electroencephalographer who also considers the clinical setting.

One can also question whether it matters if epileptic seizure activity is *the* (only) cause of the neurologic deficit. In anoxia, for example, the extent of neuronal damage is often great, and that determines the ultimate, usually disastrous, outcome [89]. Similarly, some severe metabolic derangements might suffice to explain a patient's impairment, but the seizure activity evident on the EEG might do the same in the absence of the primary illness; either process might cause the deficit. Some would label the findings "NCSE" when it is considered that a seizure with the same electrographic appearance likely *would* cause a clinical deficit if the lesion or illness were not present. Others would not.

Even after diagnosis of NCSE, the same problem persists. It can be difficult or impossible to determine whether the epileptiform waveforms on the EEG considered electrographic seizure activity contribute to or cause the clinical dysfunction.

Prolonged Duration

Many definitions of NCSE include a temporal criterion for the duration of seizure activity, or non-recovery from serial seizures. Long ago, Gastaut defined "fixed and lasting" as 30 min [84], but he was focusing heavily on GCSE.

Traditionally, for the "classic" forms of NCSE, epileptologists tended to require EEG evidence of continuous or recurrent seizure activity, along with impaired consciousness, for 30–60 min [19, 90]. For decades, most clinical studies held it useful "in the field" to consider NCSE as seizures persisting for 30 min [20].

Decades after Gastaut's early definitions, Lowenstein, Bleck and Macdonald [91] offered the first modern temporal criterion of 5 min for GCSE, establishing this as an "operational" definition—to be used largely in helping neurologists make diagnoses and determine treatment and management plans expeditiously. Their proposal was limited to apply to GCSE alone. While most neurologists have adopted this "operational" definition of GCSE, the same 5 min criterion has been used widely (if without demonstrated validity) for all types of SE in some recent publications.

The 2015 ILAE definition built on the same "operational" concept, and accepted the 5 min criterion for GCSE. It was noted, however, that different types of *nonconvulsive* SE warranted different temporal criteria: "t1" (the time beyond which seizures are unlikely to stop on their own, i.e., become SE, would be 10 min for both absence SE and for CPSE or "focal SE with impaired consciousness" [85]. For NCSE, "t2" (the time after which long-term neurologic injury would be an urgent concern and a reason for more aggressive treatment) would be 60 min for focal SE with impaired consciousness, but "completely unknown" for absence SE. For the (far more common, but quite heterogeneous) "non–classic" NCSE, or "NCSE in coma," no t1 or t2 was proposed.

A definition that includes the duration of epileptic activity is valuable for clinical ("operational") purposes: for urgent diagnosis and to promote appropriately prompt treatment in NCSE, but it does not specify its essence, or what NCSE *is*. The temporal consideration is more useful for clinical utility than for definition.

Of course, given the burgeoning multiplicity of types of NCSE, the temporal criteria cannot simply be constrained to be exactly 5 or exactly 30 min. As noted by Shorvon, NCSE is a "*range of conditions* …… dependent largely on the level of cerebral development and integrity, the presence or absence of encephalopathy, the type of epilepsy syndrome, and the anatomical location of the epileptic activity" [22]. Thus, "abnormally prolonged" focal-onset NCSE with dyscognitive features is substantially different in a young person with a genetic epilepsy and in an older patient with multiple medical problems and NCSE due to a stroke and sepsis, though they may appear similar clinically. Proper temporal criteria for the diagnosis of NCSE would be different in these two cases (and in dozens of others!), as might treatment.

In 2017 definitions of NCSE still tend to be imprecise as to its nature, but increasingly helpful "operationally." Neurologists are much more aware of its many manifestations and thus maintain a better "index of suspicion" that NCSE may be occurring and how to go about evaluating it, probably improving its recognition and diagnosis, and expediting and improving its treatment.

Classification

No classification system for NCSE will be satisfactory to all basic investigators, clinical neurophysiologists (EEG-ers), neurologists, and scholars. Gastaut stated that there were "as many types of status as there are types of epileptic seizures" [84], but the correspondence is not strict. For example, focal seizures emanate from different brain areas, with different signs and symptoms, but many can go on to generalized convulsions or GCSE, or to subsequent NCSE—with many later stages appearing similar despite the different origins.

Shorvon rejected a classification of NCSE according to seizure types noting that NCSE is not always simply the prolongation of individual seizures [92]. Different physiologic processes contribute to the initiation, maintenance, and perpetuation of SE that are not involved significantly in isolated, individual seizures. Interestingly, there are also many genetic abnormalities that correspond to epilepsy syndromes but not very well to causes of SE [93].

The 2015 ILAE Task Force proposed a diagnostic classification system based on four axes: semiology (prominent motor versus non-motor symptoms); etiology (known and unknown); EEG correlates; and age—i.e., an electroclinical organization [85]; see Chap. 2, "Types of Status Epilepticus: Definitions and Classification," for a more detailed account. NCSE is thus organized into focal and generalized forms, acknowledging that seizures can progress from a focal-onset to generalized clinical and EEG manifestations.

Different NCSE syndromes include different EEG, clinical, genetic, and developmental aspects, age-specific presentations, varied concomitant structural brain abnormalities or medical illnesses, markedly varied responses to treatment, and different longer term outcome. The ILAE proposal divided NCSE semiologically into cases in which there is preserved consciousness and others with "impaired consciousness" or impaired ability to respond appropriately to stimuli. These subdivisions are a reasonable beginning, but even given the four classification axes (with many semiologies, etiologies, EEG manifestations, and age groups), there would be scores of types of NCSE, several of which would not fit easily into simple categories semiologically, e.g., aphasic SE.

Further, there are many types or levels of "impaired consciousness." In particular, much of the "non-classic" NCSE in ICUs has persistent epileptiform discharges with quite varied gradations of diminished alertness, not just

"coma." Again, "focal SE with impaired consciousness" is different in an adolescent with mesial temporal sclerosis and in an elderly person with a stroke and metabolic derangements. Each would have different clinical settings, natures, degree of impairment (probably warranting different "t1" and "t2" times), and mandates for treatment. Classifying the many types and severities of the very common "non-classic" NCSE will remain challenging. With time, however, there will likely be many modifications and more detailed sub-classification for the many types of NCSE and one hopes, better management, treatment, and outcome.

This chapter focuses on the understanding of the nature and forms of NCSE, not on its management. Nevertheless, neurologists and other physicians must consider the potential ill effects of NCSE (i.e., pathophysiologic consequences) and plan for its treatment. Unfortunately, many earlier investigations have considered all (or large groups) of NCSE as a single entity with regard to clinical consequences and have evaluated treatments as if all varieties of NCSE were the same, possibly to the detriment of patients. As such, progress has been uneven in learning about the consequences of NCSE and about how to manage it.

Pathophysiologic Consequences

GCSE is readily recognized and, for the most part, a single entity. Clinical consequences and the likely neuronal damage from prolonged GCSE are increasingly well understood (see Chaps. 7, 9, and 10). Determining those consequences for NCSE, however, is particularly vexing, in large part because NCSE is so heterogeneous and, despite its many forms, has often been studied as if one illness (or a very few). Attempts to determine the probable pathophysiologic consequences of NCSE in humans have been difficult and frustrating.

1. Animal models are valuable and instructive regarding pathophysiologic mechanisms but sometimes of limited applicability to humans, and some models use extreme cases of persistent SE (some with greater similarities to GCSE than to NCSE), making it difficult to determine whether such dramatic forms of SE cause similar pathologic effects in humans. See Chap. 25, "Consequences of Nonconvulsive Status Epilepticus," for a more extensive discussion of this topic.
2. Biologic markers of neuronal damage may help, but in some "pure forms" of classic NCSE such as absence SE, markers such as neuron specific enolase have been elevated with little evidence of long-term ill effect [94]. There are often dramatic changes on MRI scans indicating neuronal tissue dysfunction after SE, but almost all are in cases of convulsive SE. Many follow prolonged convulsions and have underlying tissue abnormalities possibly causing the SE [95]. Also, many or most MRI abnormalities are transient rather than indicative of permanent neuronal damage. Some reports demonstrate long-term damage such as hippocampal volume loss, but almost always with convulsive SE, and often in children (with febrile and other SE) [96]. Evidence of long-term MRI abnormalities following NCSE, without prior lesions or significant medical or neurologic illnesses, is very hard to find. In the (now majority) "non-classic" cases of NCSE, some MRI changes might also reflect the harm from the underlying illnesses. In short, these markers correlate with neurologic injury, but not well enough to prove clear causality of long-term damage due to the NCSE itself.
3. Another approach would be studying the outcome of classic or "pure forms" of NCSE, such as in "idiopathic" epilepsy patients, allowing focus on the effects of seizures and NCSE without confounding by precipitating or complicating medical or neurologic illnesses. In one such study, there was essentially no long-term clinical morbidity after prolonged SE (both GCSE and CPSE) due to such "pure" epileptic seizure activity alone [97].
   Unfortunately for study purposes, however, cases of "classic" NCSE are very few in comparison to the non-classical cases of NCSE seen in ICUs today. Most "non-classic" NCSE, by its nature, is quite "impure," occurring in patients with significant neurologic or medical problems, making it difficult or impossible to control for the effects of illnesses other than the seizures or SE, themselves.
4. There has also been interest in randomized clinical trials for various forms of NCSE, seeking to demonstrate that a certain treatment will lead to better outcomes, including for neuronal damage—thereby demonstrating that the NCSE *caused* the damage. It is very unlikely, however, that such a trial can be organized. There were 570 patients in the landmark study comparing different medication treatments for GCSE, all with essentially a single form of SE (although both "overt" and "subtle") [76] while NCSE has so many forms. The heterogeneity of NCSE largely precludes randomized controlled treatment trials.
5. Possibly, the best remaining approach to this problem is studying the correlation between "seizure burden" in NCSE in critically ill patients with subsequent prolonged, stable, clinical deficits. One group found a significant correlation between duration and percentage of time in nonconvulsive seizures in critically ill children and subsequent major cognitive and clinical deficits, even when separating data into batches with different etiologies [98]. This separation is still not a perfect control for the effects of etiologies or comorbidities (and especially for the

refractoriness of the SE), but they have made major inroads. In general, they do provide support for prompt treatment of "non-classic" forms of NCSE, but they cannot instruct us on *how* aggressively to treat. See Chaps. 25 and 29 for a more complete discussion of "seizure burden."

Treatment

The management and treatment of GCSE is now relatively clearly established [76, 99]. It should be aggressive [100]. Indeed, it may be that much GCSE is treated after too long a delay and with inadequate initial doses of medication [101]. Management of NCSE, on the other hand, requires a more delicate balance in considering the consequences of the illness compared to the side effects of treatment.

For NCSE, principles of treatment and management have become much more complicated with the wider recognition of the many forms of NCSE, each of which may be treated best in an individual way, tailored to the underlying illness and the overall clinical context. Patients with "classic" forms of NCSE such as absence and CPSE seldom warrant aggressive treatment, while far more aggressive treatment with heavily sedating (or "anesthetic") drugs may be necessary in some NCSE cases, e.g., in the "special case" of NCSE following inadequate treatment of GCSE. Treating all NCSE in the same way may well produce poor outcomes [102]. A perceptive analysis on optimizing management for different types of SE is contained in a decision analysis paper [103].

Similarly, in studying the treatment of NCSE, it is extremely difficult to establish controls, not only for the many different types of NCSE and the severity of SE overall (with respect to medical and neurologic illness and comorbidities) but also for the refractoriness of the SE. For reasons still not understood well, some patients with very similar NCSE types and comorbidities have more refractory SE than others and are thus likely to be selected for more aggressive treatment.

There may be frequent undertreatment of early NCSE, and over-aggressive treatment later; 18 years after it was written, it is still reasonable to worry that NCSE is "underdiagnosed and potentially over-treated" [104]. Avoiding the ill effects of aggressive or over-treatment might be facilitated by several measures, including trying to shorten its duration. For the "non-classic" forms of NCSE, this could include quicker recognition and diagnosis, better early treatment with adequate dosing, and probably, tolerating some rhythmic epileptiform discharges and even occasional electrographic seizures, rather than intensifying suppressive treatment when they occur. Relatively high doses of "non-anesthetic" medications might be used in the attempt to taper the more highly sedating drugs used to induce "iatrogenic coma." This may involve use of moderate to high doses of shorter acting benzodiazepines such as lorazepam, or relatively high doses of phenobarbital (to which patients may habituate in terms of respiratory effort and even alertness) [105, 106]; see also Chap. 17, "Treatment of Refractory and Super-Refractory Status Epilepticus." Many alternative, non-coma-inducing therapies are also becoming available; see Chaps. 8 and 18. Finally, critically ill patients in NCSE often die because of comorbidities, especially infection, multi-organ failure, and hematologic complications [102, 107], and it is important to attend to the many medical complications that keep NCSE patients in the ICU.

As straightforward and singular an entity as GCSE is, NCSE will likely remain multifaceted, harder to define and come to grips with, and complex in its management. Given its protean nature, it is doubtful that there will be a single, precise, and universally agreed upon definition for NCSE, or a simple classification scheme. Nevertheless in 2017, definitions and classifications are improving, and there is a much richer and better understanding of what forms NCSE takes and how to recognize (diagnose) it clinically, and what may or may not represent NCSE on the EEG. Improved treatment should follow, in part through the recognition of those many forms (and clinical contexts) of NCSE, with different natures, causes, prognoses, and appropriate treatment.

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Clinical Presentations of Nonconvulsive Status Epilepticus

20

Peter W. Kaplan

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]. It should be said that within the neurological and, more particularly the epilepsy literature, the term "ictal" has often been used to refer to a process in which the presumed or proven underlying process is a state of cortical excitability. In the modern era, "ictal states" have been demonstrated on electroencephalography (EEG) in the form of status epilepticus, seizures, or even of epileptic discharges short of seizures.

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 [3], Bright [5], and Hughlings-Jackson [6], with the nature of these states remaining speculative given the lack of EEG correlate. On several occasions during his famous Tuesday morning lectures, Charcot presented a Parisian deliveryman 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 the 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 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 delirium, confusion, or psychosis.

It has been over 50 years since status epilepticus (SE) 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 5, 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

P.W. Kaplan (✉)
Department of Neurology, Johns Hopkins Bayview Medical Center, 4940 Eastern Avenue, Room 2115, 301 Building, 21224 Baltimore, MD, USA
e-mail: pkaplan@jhmi.edu

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Table 20.1 Electroencephalographic differential diagnosis of NCSE (from Kaplan [14] with permission)

Artifactual
Rhythmic, regular or paroxysmal muscle movement, ECG, or ballistocardiographic artifacts
Physiologic rhythmic patterns or patterns of nonepileptic significance
Rhythmic midtemporal theta of drowsiness
Subclinical rhythmic epileptiform discharges of adults (SREDA)
Pathologic epileptiform patterns
PLEDs [LPDs]
PLEDs plus [LPDs + F]
BiPLEDs [BIPDs]
GPEDs [GPDs]
Triphasic waves [GPDs with triphasic morphology] (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)

ECG electrocardiogram
PLED periodic lateralized epileptiform discharges
LPD lateralized periodic discharges, GPD generalized periodic discharges
BiPLED bilateral independent periodic lateralized epileptiform discharges
GPED bilateral synchronous epileptiform discharges

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, or deep coma.

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), more recently classified as lateralized periodic discharges (LPDs); 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 20.1) [14]. 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 [12], and hence such cases remain *probable* NCSE rather than *definite*.

Classification

Prior classifications of status epilepticus have been suggested on the basis of etiology, clinical phenomenology, pathophysiology, and EEG characteristics [15]. More recently, the Commission of Classification and Terminology of the International League Against Epilepsy charged a Task Force with revising the classification of status epilepticus. This group in turn created a classification based on four axes: (i) semiology, (ii) etiology, (iii) EEG correlates, and (iv) age [16]. Various forms are differentiated along taxonomic lines into *motor activity*, and *impairment of consciousness*, producing two major groups: [1] status epilepticus with prominent motor symptoms, including all convulsive forms, and [2] those without prominent motor forms representing non-convulsive forms of status epilepticus (NCSE). Each group can be subdivided by the degree of consciousness impairment, while etiology divides into: (i) known or symptomatic (also subdivided into acute symptomatic, remote symptomatic and progressive symptomatic), and (ii) unknown or cryptogenic. Known causes of

status appear as an appendix. The third axis comprises EEG correlates—more important in NCSE. Descriptors adopted (such as morphology, location, time-related features) were adopted from those developed by the American Clinical Neurophysiology Society [17]. Nonconvulsive status epilepticus (NCSE) had previously been divided into two groups, largely along electroencephalographic criteria:

1. Absence status epilepticus (ASE), a form of generalized nonconvulsive status epilepticus (GNSE)
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
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 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 types of NCSE based on localization-related EEG criteria as well as age of expression and particular epileptic syndromic context is provided in Table 20.2. Many of these features are superseded by the latest classification of the Task Force, but are provided, as they are familiar to many clinicians of the past two decades.

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 [or LPDs]), bilateral independent periodic lateralized epileptiform discharges (BiPLEDs [or BIPDs]), or even bilateral synchronous epileptiform discharges (GPEDs [or GPDs]), all of which may be seen in cortical hyperexcitable states that may follow seizures in a patient with a structural abnormality, or in patients with encephalitis (For updated terms for the types of periodic discharges (LPD, GPD, BIPD), see Hirsch and colleagues [17]). 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 epileptic or "ictal." Nonetheless, this borderline is a "gray zone" because epileptic activity may not particularly originate in the motor cortex so as to produce clonic activity; conversely it may represent the end of the electroclinical continuum that follows convulsive status epilepticus [18].

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 (GPDs with triphasic morphology). In this

Table 20.2 Classification of nonconvulsive ictal states (from Kaplan [14] with permission)

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)
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 LPDs[a]) or PLEDs plus LPDs-plus[a]
ii. Confusion, with bilateral independent periodic lateralized epileptiform discharges (BiPLEDs or BIPDs[a])
iii. Confusion, with bilateral synchronous epileptiform discharges (GPEDs or GPDs[a])
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)]

[a]For updated terms for the types of periodic discharges (LPDs, BIPDs, GPDs) see Hirsch and colleagues [17]

way, these states resemble, and can be confused with, NCSE, even to the point of suppression of "ictal" triphasic-wave activity after IV benzodiazepines.

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 [15, 16, 18–77]. 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 the 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 [42]. Similarly, stereotyped, complex automatisms are also more frequent in CPSE [42]. Lip-smacking, other oroalimentary automatisms, lateralized limb automatisms, and dystonic posturing, eye deviation, and nystagmus are typical of CPSE [38, 42–44]. 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 300+ patients with NCSE have been identified over the past 30 years, the diagnosis was frequently delayed or even missed [12, 40]. Table 20.3 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 20.4 (see also Chap. 2, "Types of Status Epilepticus: Definitions and Classification").

Clinical and Behavioral Correlates of NCSE

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 [45, 47]. Three quarters of the cases appear before the age of 20 years, and in a third, TAS heralds epilepsy [47]. The typical clinical features described in the absence status epilepticus are given in Table 20.5.

Typical absence status epilepticus starts abruptly and without warning (see Chap. 15, "Status Epilepticus in the Idiopathic Generalized Epilepsies"). Typical features include perioral myoclonus, myoclonic eyelid twitching, mild to marked obtundation, bradyphrenia and bradykinesia, and confusion [47]. The change in responsiveness can be highly variable, an illustration of which is provided in Fig. 20.1 [56]. 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 [47]. Such descriptions can be seen in the subsection "Experiential" in Table 20.5. The following are typical experiential accounts of TAS

Table 20.3 Clinical examples in which the diagnosis of NCSE was missed or delayed (from Kaplan [14] with permission). Data from Johns Hopkins Bayview Medical Center, Baltimore, Maryland, USA [12, 40]

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

Table 20.4 Differential diagnosis of NCSE (from Kaplan [14] with permission)

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, cefepime
Epilepsy/Seizure-related
Typical absence status epilepticus
Atypical absence status epilepticus
Lennox-Gastaut syndrome with encephalopathy
Altered mental states with PLEDs (LPDs)/GPEDs (GPDs)/BiPLEDs (BPDs)
Prolonged postictal confusion
Epileptic fugue states/poriomania
Interictal/postictal psychosis
Psychiatric
Acute psychotic reactions
Somatoform disorders
Dissociative conversion reactions
Malingering

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 [47].

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 [47].

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" [47]. Other descriptions include a "feeling of uncontrollable rush of thoughts and fear of the loss of control of the mind." One patient 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 [47].

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

Table 20.5 Clinical features described in absence status epilepticus (from Kaplan [14] with permission)

Attitude	**Behavior**
Unreactivity to threat	Inappropriate for situation with preserved alertness
Lack of initiative	Infantile behavior
Inability to plan	Fugue states
Withdrawal	Catatonia
Affect	**Psychiatric**
Indifference	Hallucinations
Perplexity	Paranoid persecution
Crying	**Experiential**
Laughing	Feeling of oppression
Aggressivity	Uncontrollable rush of thoughts
Memory/Cognition	Desire to (but inability to) perform simple motor acts (motor apraxias)
Variable amnesia	Dreamy state: "feels vague"
Slow ideation	"In a different world"
Disorientation	"Drifting away"
Speech	"Drunk"
Verbal perseveration	Worried; edgy
Monosyllabic answers	Dizzy
Lack of spontaneous speech	Missing pieces of conversation
Interrupted speech	Central vision "vibrates"
Clicking noises in mouth	**Other**
Motor	Incontinence
Hippus	Diarrhea
Clumsy motor performance	Headache
Motor perseveration	Frontal release signs
Automatisms (chewing; compulsive handling of objects)	Babinski reflex
Rhythmic blinking	
Eye rolling	
Small amplitude jerking of face or arms	
Quivering of lips	
Tonic neck spasms	
Ataxic gait/pseudoataxia	
Wandering	

appear introverted or frankly disoriented. One patient described a feeling of "closeness" or "heat" [47]. 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 [78]. Before and after NCSE, his ability to draw a clock face changed markedly (Fig. 20.2). 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 [47].

TAS may present with aggression, impulsive behavior, agitation, and hostility [45, 52]. 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 [44]. 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

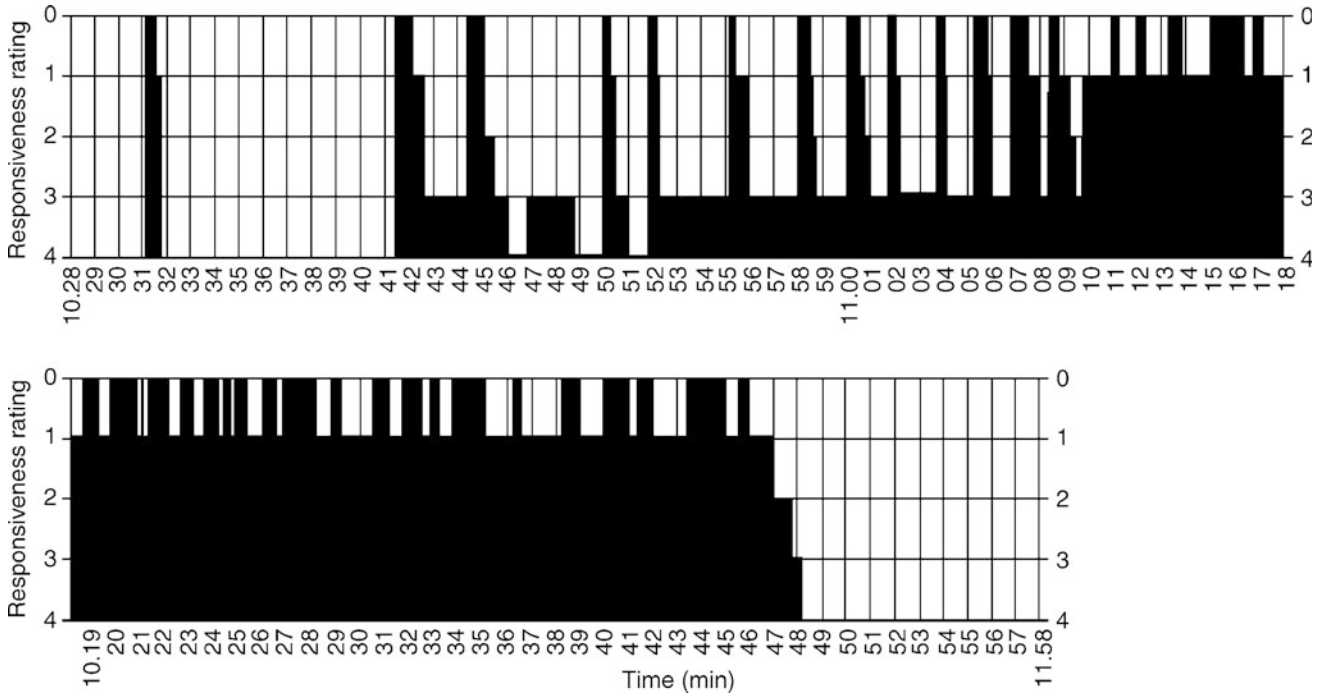

Fig. 20.1 Responsiveness during petit mal status. The patient has a brief absence attack at 10:31 AM, then a series of attacks beginning at 10:41 AM, with intervening periods of normal responsiveness. She had severe impairment of responsiveness from 11:10 to 11:48 AM, and then made a sudden recovery 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 initiates conversation, responds with more than one or two words. From Theodore and Porter [56] with permission

and off [45]. Even amidst apparent confusion, some patients will retain much that takes place and be able to carry on relatively complex activities [45].

Clouding of consciousness can obscure other more typical and, therefore, diagnostic clinical features. Dunne and colleagues [41] 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 20.6 [42]. Contrasting with CPSE, TAS typically induces little amnesia, and there is little postictal confusion after the event [45]. 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 [45].

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 "dysfunctional days" with level of consciousness particularly affected. Such changes in consciousness with AASE are given in Table 20.7 [57]. Unlike in TAS, convulsions rarely herald or terminate AASE. About 50% of patients

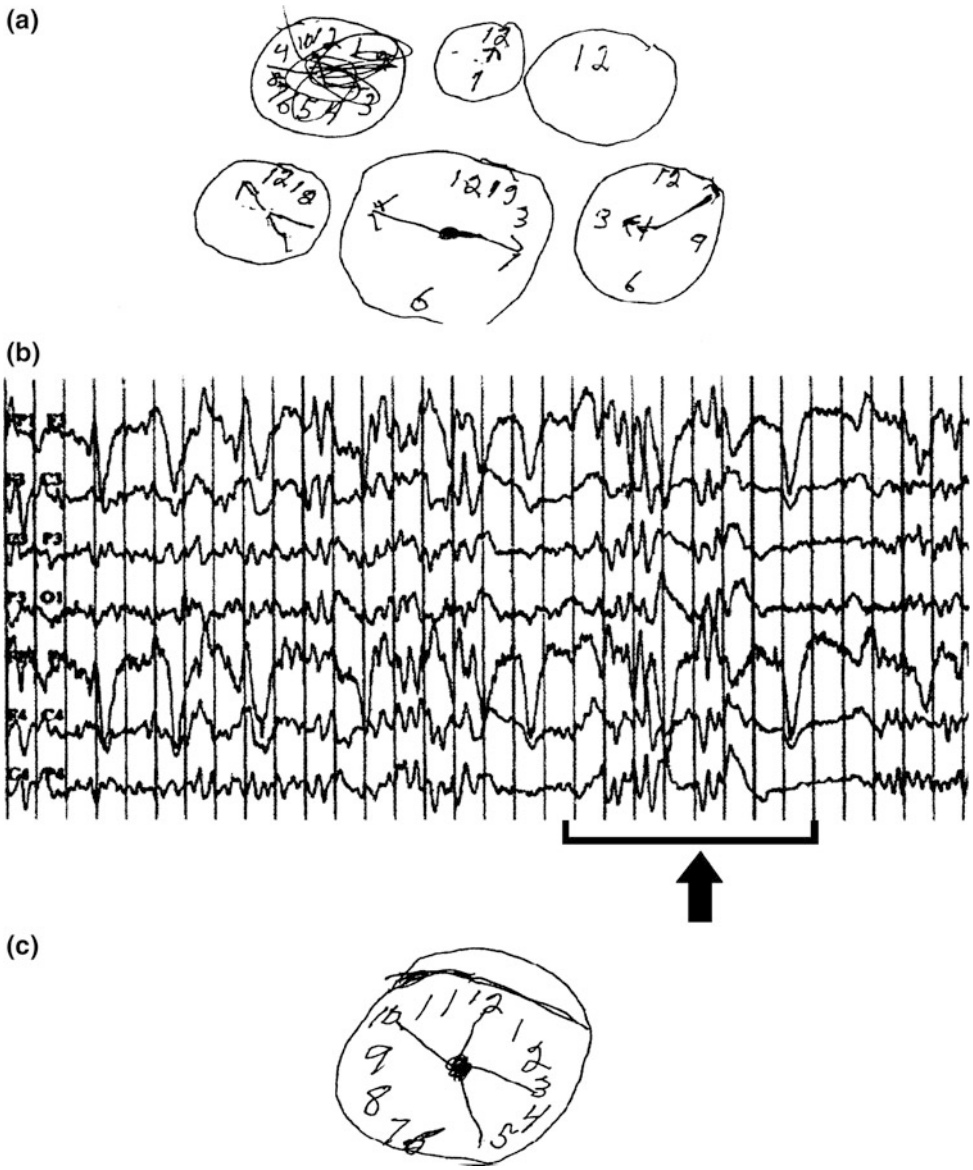

Fig. 20.2 **a** Patient's effort to draw the face of a clock during nonconvulsive status epilepticus (NCSE) with EEG as seen in 2B. **b** EEG during NCSE showing runs of bilateral, synchronous polyspike-slow-wave complexes. **c** After treatment of NCSE with lorazepam, patient is able to draw a better clock. From Olnes et al. [78] with permission

may have perioral, facial, or limb myoclonus [44, 57]. Further discussion on characteristics of AASE is in later paragraphs.

Simple Partial Nonconvulsive Status Epilepticus

Simple partial nonconvulsive status epilepticus (SPNSE) may be difficult to prove (see also Chap. 21, "Cognitive Manifestions of Focal Status Epilepticus"). 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, 58–61]. Autonomic and vegetative features may appear, including ictal fear, anorexia, weight loss [58], and poorly described visceral sensations [7]. There may be mild confusion, bad-tempered behavior, depression, or even suicidal ideation with an anterior temporal focus [59]. A temporal focus may also engender inchoate fright [60]. More posterior ictal foci in the temporo-parieto-occipital junction may induce adversive eye movements with stepwise contraversive nystagmus [61]. Right-hemisphere SE may be barely perceptible by clinical examination, and only identified by careful neuropsychologic testing [62]. 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 [63]. Transient cortical blindness may occur

Table 20.6 Behavioral distinctions among absence, temporal lobe complex partial, and frontal lobe complex partial status epilepticus (adapted from Rohr-le Floch and colleagues [42] with permission)

	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

[64]. Although simple partial SE is frequently presumed in the absence of EEG evidence, all published cases are supported by an EEG correlate [7].

Complex Partial Status Epilepticus

The first case of CPSE was probably described by Gastaut and Roger in 1956 [9], but by 1983 only 17 clearly identified cases had been published [39]. However, with increasing use of video EEG recording, hundreds of cases have been identified since [65, 66]. Nonetheless, it is probably an under-recognized entity [32, 65]. Other terms used to describe CPSE include temporal lobe status epilepticus, prolonged epileptic fugue, psychomotor status epilepticus, prolonged epileptic twilight state, or even poriomania [20, 21, 24, 25, 27, 39, 67].

CPSE can broadly be described as abnormal behavior or level of consciousness associated with lateralized seizure activity, with impairment of consciousness ranging 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 [32, 68].

Table 20.6 illustrates the great variability in clinical correlate with CPSE from changes in affect, "ironic smiles," Wernicke aphasia [69], or even fugue states. The typical marked changes in level of responsiveness over time are characterized in Fig. 20.3.

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 [38, 46, 48, 59, 70], both cycling and continuous clinical presentations have been described with ASE [38, 42–44], requiring other clinical characteristics for

Table 20.7 Alteration of consciousness as a manifestation of atypical absence status epilepticus (from Roger and colleagues [57] with permission)

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	

a clear clinical differentiation. With the hundreds of 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 amygdalo-hippocampal 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 [70, 73]. Some patients were totally unresponsive, with motionless staring; others had alimentary automatisms, vocalizations, and perseverative gesticulations [70].

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 [70]. 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 [70]. 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 [70]. 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 [61]. 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 [70]. Williamson described a patient studied with depth electrodes who clinically manifested verbal unresponsiveness, confusion, and head and eye deviation, and yet localization lay in the hippocampus [66]. 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 [66].

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" [19, 24, 25]. 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" [19, 24, 25, 62, 74–77]. Work by

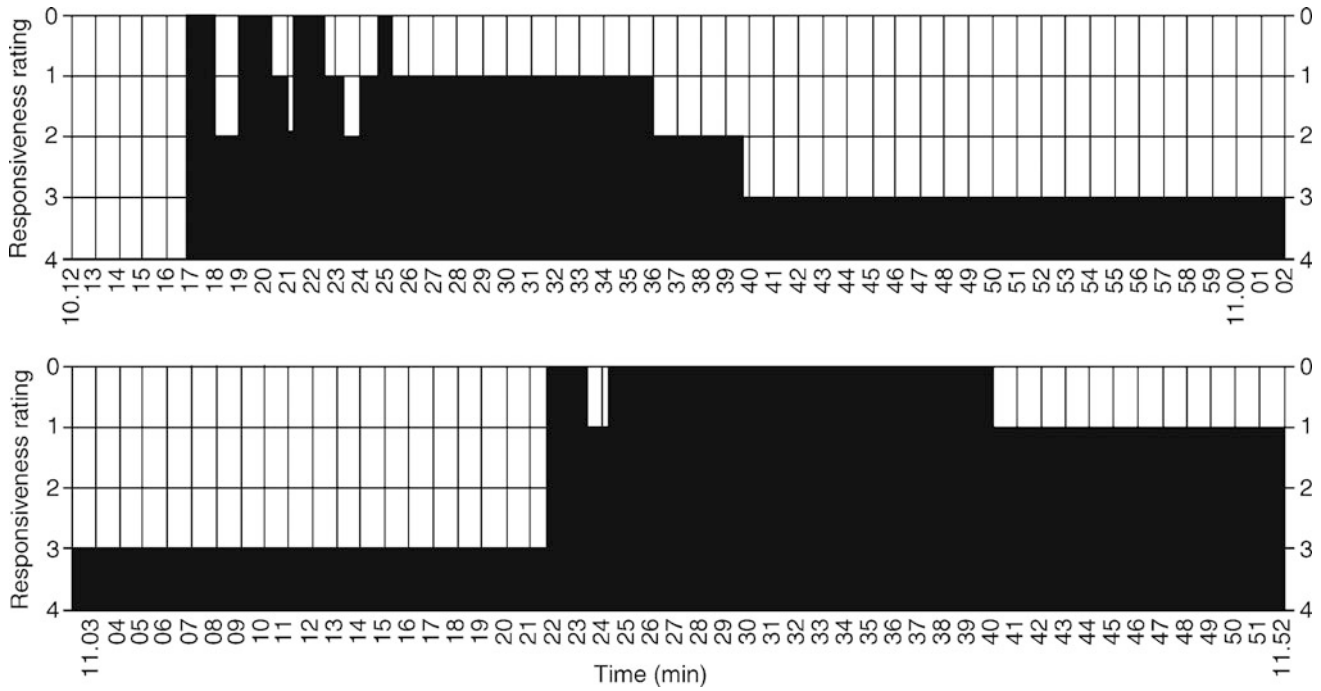

Fig. 20.3 Responsiveness during complex partial status. The patient had a complex partial seizure at 10:17 AM and did not recover normal consciousness until several hours later. He had several attacks at the onset of status (10:17–10:25 AM), then appeared to be gradually recovering, but had another series of attacks beginning at 11:22 AM. Recovery occurred gradually. The responsiveness rating is the same as in Fig. 20.1. From Theodore and Porter [56] with permission

Rohr-le-Floch and colleagues [42] and Thomas and colleagues [27] have revealed more of the subtle differences distinguishing frontal CPSE from ASE (see Table 20.6).

With frontal lobe CPSE (FLCPSE), there is generally a lesser impairment of consciousness, and fewer fluctuations [42]. 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 [42].

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 I had affective disinhibition or indifference, subtle impairment of cognition and mood disturbances, but with no overt confusion [27]. 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 7 s, 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 [27]. Patients were noted at times to have a blank facial expression, lack of spontaneous emotion, and decreased verbal fluency [27]. Fluctuations in these clinical features 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 [27].

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 [79, 80]. As noted by Thomas and colleagues, no subjective or objective cognitive sequelae were seen after type I FLCPSE.

The rarer type II FLCPSE had greater impairment of consciousness associated with bilateral frontal foci [27]. 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 [27].

NCSE Presenting in Infancy, Childhood, and the Elderly

Neonatal nonconvulsive status epilepticus differs from its clinical expression at other ages (see Chap. 16, "Early Treatment of Generalized Convulsive Status Epilepticus"). 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 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 20.8.

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 [81–83]. Nonconvulsive states may also occur over the occipital regions, with nausea, anorexia, and visual hallucinations.

NCSE in the Developmentally Delayed

Electrical status epilepticus during slow-wave sleep (ESES) typically occurs in developmentally delayed children during nighttime sleep (see also Chaps. 26 through 28). Characteristic spike-wave discharges occur during at least 85% of non-REM sleep [7], with seizures appearing between ages 1 and 14 years. 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 [84, 85]. It is not known whether the EEG is an epiphenomenon of the encephalopathy or the

Table 20.8 Clinical features of NCSE in infants and children (from Kaplan [14] with permission)

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

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 years. 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 [15]. From the behavioral perspective, the patients appear to have frontal lobe seizures, although the EEG localization interictally is more variable [15]. Most patients appear to have either Lennox-Gastaut syndrome or Landau-Kleffner syndrome [15]. During later childhood, one can recognize the more classic clinical presentations of NCSE in the form of AASE and CPSE, as described above. Stores provide 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" [18].

The patient may bump into objects, walk into doors, and exhibit poor balance and poor control of movements, and have frequent falls [18]. These clinical features have been referred to as *pseudodementia* and *pseudoataxia*. Clinical features are provided in Table 20.9.

Ring chromosome 20 with NCSE has been delineated in patients from Japan between the ages of 13 and 31 years [86]. 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.

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. 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.

NCSE in the Elderly

NCSE in the elderly, delineated by Thomas and colleagues, usually affects a different patient substrate [23, 87–90]. It occurs in the setting of metabolic dysfunction, 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 days [23]. Morbidity and mortality may reach almost 60% [87–90]. Clinical features included "interrupted speech, catatonia, slow and ataxic gait." There are reports of chewing and compulsive handling of objects, frontal release signs, and Babinski reflexes. Almost three quarters of patients above the age of 40 years are women [89, 90], with typical triggers including drug withdrawal, toxic or metabolic dysfunction, and the use of neuroleptic, psychotropic medications, particularly the benzodiazepines. Two-thirds of the patients have moderate impairment of consciousness with unresponsiveness, staring and waxy rigidity, severe language problems to the point of mutism, and verbal perseveration [90]. Patients may be agitated, aggressive, hallucinating, and emotionally labile. Frequent minor motor accompaniments are twitching of the eyelids, mouth, and limbs [90].

Psychiatric Features and Presentations

Although psychosis has a prevalence rate of 1% in the general population, it ranges from 3 to 7% in patients with epilepsy. The ictal psychotic symptoms resemble schizophrenia, and symptoms are treated similarly. With partial seizures, psychiatric features have long been recognized, including visual or auditory hallucinations and illusions, fear, paranoia, and agitation. There may be affective changes, a sense of de-realization and depersonalization, and seeing oneself (autoscopy) [91]. With NCSE, the psychiatric and behavioral manifestations may range from catatonia to manic hyperactivity. Psychotic features may be florid. One patient perceived himself to be in a warped mirror and heard voices ordering him to take the poison off his body (he had worked as a horse keeper) [91]. Another patient would leave work to take photographs of women on the train and hence

Table 20.9 Clinical features of NCSE described in developmental delay (from Kaplan [14] with permission)

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

received a police warning [92]. The type I FCPSE discussed above, with a right-sided focus may result in hypomania, an increased verbal output and affective disinhibition [14, 27]. Conversely, left-sided foci may produce a masked facies, decreased verbal fluency, flattened emotional states, and a decrease in motor activity. Overt confusion may be absent! In the elderly, many of these clinical signs may be missed.

Some conditions that independently have psychiatric manifestations, may also result in NCSE. Patients with mitochondrial encephalopathy, lactic acidosis and stroke (MELAS) may have confusion and aggression, but a patient with associated NCSE had paranoid ideation, tangential thinking, delusions, psychomotor retardation, and impaired insight, judgment, and motivation [93].

Conclusion

It has been 80 years since a clear EEG correlation to nonconvulsive SE was first made, followed by a steadily 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, sensation, movement, the special senses, the psyche, and level of consciousness.

NCSE is under-recognized and underdiagnosed, often because of its similarity to, and mistaken diagnosis for, specific disorders of the symptomatic body parts—e.g., vegetative complaints attributed to gastro-intestinal problems; a speech deficit thought to be due to a stroke with aphasia; or psychosis believed to be a primary

psychiatric disorder. There are often marked delays in requesting an EEG, and hence in making the correct diagnosis of NCSE. Many of the features of NCSE have even been attributed to psychogenic states or conversion disorders. With clinical vigilance, the availability of EEG, and knowledge of the pleomorphic clinical presentations, physicians should be able to diagnose and manage the great clinical and EEG spectrum of NCSE.

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Cognitive Manifestations of Focal Status Epilepticus

21

Vaishnav Krishnan, Frank W. Drislane, and Michael G. Benatar

Introduction

The clinical manifestations of focal seizures are usually determined by the specific anatomic location of origin and the spatial and temporal propagation of hypersynchronous excessive neuronal activity [1]. Seizures originating in or involving motor or premotor regions are most easily recognized, as they typically cause "positive symptoms" which are broadly termed "convulsive" such as parosysmal jerking, twitching, or tonic or clonic movements of the contralateral limb. Similarly, epileptic activity (whether frequent epileptiform discharges or more prolonged electrographic or clinical seizures) that remains localized within brain regions or networks devoted to specific cognitive or emotional functions can produce a variety of focal cognitive or emotional derangements (Table 21.1) [2–15]. Such "ictal" (defined here as related to or occurring during the course of epileptic seizure activity) focal cognitive symptoms and signs represent an important diagnostic and therapeutic challenge to emergency room physicians, neurologists, and epileptologists for three main reasons. First, when patients do not display or report convulsive movements or frank impairment of consciousness, clinicians must possess a high index of suspicion for an underlying primary epileptic etiology and perform a systematic cognitive evaluation as part of the screening neurologic examination. Second, as discussed below, while underlying epileptic activity may be paroxysmal or wax and wane in intensity, focal cognitive symptoms can be more chronic or persistent, possibly because "ictal" and "post-ictal" behavioral expressions may be similar (e.g., a mixed aphasia). Thus, patients often present with a new onset persistent deficit, leading to an urgent evaluation for an ischemic or hemorrhagic stroke. Third, attributing focal cognitive symptoms to an underlying epileptic etiology requires the demonstration of temporally correlated focal epileptiform discharges, electrographic seizures, or in certain instances, rhythmic slowing on scalp electroencephalography (EEG). This sets up a *catch-22,* in that scalp EEG typically lacks the spatial resolution and sensitivity to detect up to 80% of simple partial seizures reliably [16]. This forces clinicians to rely on other methods to demonstrate the presence of such epileptic activity, ranging from therapeutic trials of antiseizure drugs (ASDs) to using neuroimaging modalities such as SPECT (single photon emission computed tomography) capable of demonstrating focal regions of ictal hypermetabolism.

Through a series of illustrative case examples, this chapter explores various cognitive manifestations of focal seizures and focal status epilepticus (see Table 21.1). The chapter is divided into sections based on seizure semiology, with particular emphasis on epileptic aphasia and amnesia, as examples of focal cognitive symptoms referable to seizure activity within the temporal lobes. Subsequently, seizure-induced psychosis, depression, and fear or panic are described as examples of how focal seizures may result in pure psychiatric symptoms without impairment in language or attention. We caution readers to avoid the tendency to distinguish focal seizures based on the presence or absence of impaired awareness or consciousness (i.e., with or without "dyscognitive features" [17]). A clinically meaningful definition of consciousness has proven elusive [18] and may be difficult to assess reliably, particularly when focal impairment of language function and memory may interfere with these activities. We agree with the recommendations of the International League Against Epilepsy, which approaches *all cases* of status epilepticus as occurring within specific axes of (i) Semiology, (ii) Etiology, (iii) EEG correlates, and (iv) age [19].

For reasons described above, the literature on focal cognitive dysfunction explicitly due to status epilepticus is somewhat narrow and limited to case reports and case series. For the purposes of understanding the spectrum of cognitive

V. Krishnan (✉) · F.W. Drislane · M.G. Benatar
Department of Neurology, Harvard Medical School, Beth Israel Deaconess Medical Center, Neurology, 330 Brookline Avenue, Boston, MA 02210, USA
e-mail: vkrish@bidmc.harvard.edu

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Table 21.1 Cognitive and behavioral manifestations of nonconvulsive seizures

Cognitive sign	Definition	References
Asomatognosia	Failure to recognize a body part as being one's own	Thomas et al. [2], Feinberg et al. [3] and Nishibayashi et al. [4]
Anosagnosia	Lack of awareness of a neurologic deficit despite attempts to bring the deficit to the attention of the affected individual	Grand'Maison et al. [5]
Catatonia	Behavioral unresponsiveness associated with motor immobility	Lim et al. [6] and Kanemoto et al. [7]
Alexia	Impaired reading	Kutluay et al. [8]
Agraphia[a]	Impaired writing	Schomer et al. [9] and Matsuoko et al. [10]
Acalculia[a]	Impaired calculation	Matsuoko et al. [10] and Shimotake et al. [11]
Left-right confusion[a]	Uncertainty regarding which side is right and which is left	Matsuoko et al. [10] and Shimotake et al. [11]
Finger agnosia[a]	Inability to recognize and name individual fingers	Matsuoko et al. [10]
Apraxia	Impairment of a learned motor task in the absence of an underlying motor, sensory or other cognitive defect	Matsuoko et al. [10] and Profitlich et al. [12]
Echolalia	Inappropriate repetition of verbal stimuli (words, phrases and/or full sentences)	Linetsky et al. [13] and Cho et al. [14]
Hemineglect	Deficit in attending to, or being aware of one side of space or one's own body	Schomer and Drislane [15]

[a]Typically occurring in the context of Gerstmann syndrome

disturbances that may result from focal seizure activity, the temporary cognitive manifestations of short-lived seizures are approximated as being representative of the more persistent focal cognitive dysfunction that may occur in the setting of focal status epilepticus. Furthermore, because the term *status epilepticus* implies either ongoing prolonged seizure activity or recurrent seizure activity with incomplete recovery in between seizures, it is worth noting that specific cognitive changes may occur either as ictal or post-ictal manifestations.

Ictal Aphasia

Introduction

Aphasia, broadly defined as abnormal language function, can be the sole expression of a focal seizure or focal status epilepticus. Ictal aphasia is often *mixed* (with deficits in comprehension, fluency, and repetition) or may impair individual language functions specifically, such as naming, syntax, or grammar, and in subtle cases may be reflected as intermittent paraphasic errors only. These may be either *semantic paraphasias* (where the intended word is replaced by a word of a similar meaning, such as *blouse* instead of *shirt*) or *phonemic paraphasias* (where a word is replaced by another with a similar sound, such as *duck* instead of *truck*). Ictal impairment of language function may spare verbal fluency and comprehension entirely and may selectively impair reading (*alexia*), writing (*agraphia*), or both.

Reductions in speech *quantity* or verbal output are often the first clue to the presence of an aphasia, but it is important to recognize that not every patient with diminished speech has an underlying language disorder. Examples include failures of speech production due to primary impairment in consciousness (e.g., coma or obtundation), or severe speech *apraxia* or impairment in buccofacial muscle activity, due to central or peripheral etiologies. Reductions in arousal and attention that are central features of toxic and metabolic encephalopathies may produce reductions in verbal output in association with other clinical features such as *abulia* and intermittent agitation and are seen commonly in hospitalized patients with metabolic derangements. Nevertheless, true paroxysmal aphasia does occur in the setting of encephalopathic states and may represent an epileptic phenomenon or the clinical *recrudescence* of the effects of a known structural lesion (e.g., old infarction) which led previously to transient aphasia.

Phenomenology of Ictal Aphasia

Many reports of ictal aphasia do not provide the results of detailed language testing, and thus do not provide a

comprehensive assessment of clinical phenomenology. Ictal aphasia may be an uncommon entity, but in many instances, underreporting occurs for various reasons. For example, if the subject is asleep or obtunded and no effort is made to prompt speech, reading, or writing during a seizure arising from the relevant brain region, there may be no overt manifestations of aphasia. A related difficulty that may lead to under-recognition of ictal aphasia is the presence of more striking coincident motor activity, such 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.

Table 21.2 [20–38] summarizes a series of select cases of ictal aphasia. Where possible, details of language testing have been designated as Broca's, Wernicke's, mixed, or transcortical. Where the features suggest a Broca's or Wernicke's aphasia but the ability to repeat is not tested, the designations "anterior" and "posterior" have been used. In several of these cases, aphasia was due to underlying status epilepticus. A few conclusions may be drawn from these case reports. First, virtually every type of aphasia may occur as a clinical manifestation of seizures or status epilepticus. Second, various electrographic correlates can be seen, ranging from lateralized periodic discharges (LPDs) to high voltage rhythmic slowing. Third, there does not appear to be a characteristic feature of ictal aphasia that can be used to distinguish it from aphasia due to other causes. In a minority of cases, other paroxysmal seizure symptoms were seen (e.g., clonic limb movements, olfactory hallucinations, post-ictal impaired consciousness, etc.) that suggested an underlying epileptic origin. Fourth, a correlation between the spatial location of 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 may or may not be seen on conventional neuroimaging.

Post-ictal Aphasia

Documenting the presence and degree of post-ictal aphasia can provide tremendous lateralizing value in the evaluation of patients with medically refractory temporal lobe epilepsy, particularly in those patients in whom (i) interictal epileptiform discharges are bilateral, or (ii) complex partial seizures, presumably emanating from temporal regions, have a very limited scalp representation. In a prospective study of 105 seizures recorded from 26 patients, all of whom progressed to have identification of the seizure focus confirmed by successful temporal lobectomies, all 62 seizures originating from the dominant temporal lobe were associated with a significant *post-ictal language delay* (PILD). This was assessed by presenting promptly a phrase from the Boston Diagnostic Aphasia Test ("They heard him speak on the radio last night") on a placard in large bold print. Following left (i.e., language dominant) temporal seizures, patients required more than 68 s to read the phrase correctly, in contrast to under 54 s for seizures arising from nondominant temporal regions, with similar findings observed when post-ictal paraphasias were assessed quantitatively [39]. These results have been replicated [40], and follow-up studies have demonstrated the value of simple but systematic post-ictal language testing in identifying frontal lobe complex partial seizures that spread to the adjacent temporal lobe [41]. Interestingly, a majority of patients with psychogenic nonepileptic seizures reported that they either "couldn't read" the phrase or that the words were "blurry," a finding not seen in patients with true temporal lobe seizures [42]. These results confirm the importance of systematic post-ictal language testing in patients with complex partial seizures.

Landau–Kleffner Syndrome

A chapter dealing with ictal aphasia would be incomplete without reference to the Landau–Kleffner syndrome, defined originally as "a syndrome of acquired aphasia with convulsive disorder in children" [43]. In this syndrome, a language disorder is thought to be caused directly by epileptic discharges in regions of the brain critical for normal language function. The anatomic boundaries of the syndrome are not well defined. The classic history 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 years [44]. The 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. Clinically overt seizures are uncommon. The waking EEG is often normal, and a key finding in this syndrome is the presence of very frequent spike and wave discharges during sleep. The topography, abundance, and persistence of spike and wave discharges vary among patients and at different stages of the syndrome. Additionally, during the course of the illness, patients inevitably display continuous spike/wave discharges (bilateral or generalized) during slow wave sleep (CSWS). While traditional antiseizure drugs remain first line therapy, the use of corticosteroids tends to produce more longlasting benefits [45]. In certain extreme cases, surgical treatments (such as multiple subpial transection) have been undertaken, though often without clear benefit [46]. This syndrome 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 relevant brain regions.

Table 21.2 Phenomenology of individual cases of ictal aphasia with associated clinical and EEG characteristics

References	Type of aphasia	Other ictal features	Ictal EEG	Response to ASDs
Rosenbaum et al. [20]	Broca	Right hemiparesis and numbness; clonic movements of jaw and right hand	L centroparietal rhythmic activity 12 Hz activity	Not reported
Hamilton and Matthews [21]	**Anterior**	Right facial weakness	Paroxysmal L frontal and anterior eplileptiform activity	No speech recovery between EEG bursts of seizure activity
Wells et al. [22]	**Mixed**	Mild right pronator drift	L rhythmic 14 Hz sharp waves	Abrupt response
Kirshner et al. [23]	**Transcortical sensory**	Acalculia	Frequent L temporal ictal activity	Gradual improvement
Knight and Cooper [24]	Wernicke	None	Bursts of L temporal poly-spike and slow wave	Gradual improvement
Racy et al. [25]	Mixed	None	L temporal delta and sharp waves	Gradual improvement
Racy et al. [25]	Posterior	None	Continuous 1/2–1 Hz L temporal sharp waves	Not reported
Dinner et al. [26]	**Mixed**	None	Bursts of L temporal 11–12 Hz sharp activity	Gradual improvement
Smith Doody et al. [27]	Wernicke	None	Pseudoperiodic L temporal 1–3 Hz spike and slow waves	Not reported
De Pasquet et al. [28]	**Wernicke**	Single clonic seizure of right arm	L frontotemporal 6–7 Hz activity	Mild persistent aphasia
Grimes and Guberman [29]	**Mixed**	Rightward gaze	L temporal seizures	Abrupt response
Suzuki et al. [30]	Mixed	Sometimes followed by ↓ arousal	L fusiform gyrus seizures	Not reported
Abou-Khalil et al. [31]	Mixed	Olfactory hallucinations	L temporal ictal discharges	Not reported
Primavera et al. [32]	Global	None	Rapid low voltage activity, then spikes, and then slowing	Gradual improvement
Spatt et al. [33]	**Global**	Simple auditory hallucinations	Paroxysmal L temporal sharp activity	Gradual improvement
Murchison et al. [34]	**Wernicke/global**	None	Runs of high amplitude irregular activity	Abrupt response
Gilmore and Heilman [35]	Broca	Mild right facial, orobuccal, and hand apraxia	L frontocentral and temporal ictal discharges	Abrupt response
Tokushige et al. [36]	**Mixed**	None	L parieto-occipital high voltage delta waves	Gradual improvement
Flügel et al. [37]	**Mixed**	Mild right pronator drift	L hemisphere high voltage slowing	Not reported
Sadiq et al. [38]	Broca	Aleia, agraphia	L temporal discharges	Rapid improvement

Bold font indicates that aphasia was due to status epilepticus
L left, *R* right, *ASD* antiseizure drug

Conclusion

Ictal and post-ictal aphasia can vary in phenomenology and severity, ranging from subtle paraphasic errors to global aphasia with mutism. In cases of new onset aphasia, continuous EEG (C-EEG) monitoring is necessary to identify electrographic correlates, which may themselves be quite subtle (e.g., rare discharges) and may not unambiguously differentiate between ictal and post-ictal states (e.g., rhythmic or hemispheric slowing). Together with a comprehensive neurologic examination and C-EEG video monitoring, neuroimaging studies (which include measures of perfusion) may help distinguish between aphasia related to transient ischemia and an underlying epileptic etiology.

Ictal Amnesia

Introduction

The relationship between seizures and memory dysfunction is complex. Memory impairments are common in patients with epilepsy and are likely mediated by a variety of factors, including the long-term disruptive effects of seizures on memory circuits, the cognitive dulling effects of most ASDs, poor sleep, and in some cases, the underlying epileptogenic lesion itself [47, 48]. Aside from these interictal deficits, many focal seizures with "dyscognitive" features are themselves associated with some degree of amnesia for the events that transpire during the seizure. Whether this transient amnesia is a result of impairment in arousal, attention, or perception, however, is difficult to ascertain. Can seizures result in an isolated deficit in memory function without a more diffuse impairment in cognition?

Before answering this question, some terminology should be clarified. *Working memory*, also known as short-term memory, describes the active "on-line" holding and manipulation of information, and is largely subserved by frontal and prefrontal circuits. *Long-term* memory, on the other hand, refers to information that is stored "off-line" for periods varying from minutes to years. Long-term memory can be further subdivided into *explicit* (also termed *declarative* memory, for events, facts, meanings, and concepts of the external world) and *implicit* (also termed *nondeclarative* or *procedural* memory, for actions, skills, and habits). The formation of stable long-term declarative memory is facilitated primarily by the hippocampus, receiving input from an array of cortical and subcortical regions through entorhinal, perirhinal, and parahippocampal cortical regions [49]. Accordingly, selective bilateral hippocampal lesions (such as those following limbic status epilepticus [50, 51]) result in persistent *anterograde amnesia*, occasionally associated with hyperphagia and hypersexuality (the Kluver–Bucy syndrome, [52]). Procedural memory formation is encoded by extrahippocampal circuits, including the striatum, motor cortex and the cerebellum, and is often spared in bilateral temporal lesions [49]. In contrast, *retrograde amnesia* refers to the inability to recall previous memories that have already been established. As can be expected, testing objectively for retrograde amnesia is difficult to standardize (as patients may vary in their knowledge of previous events). Retrograde amnesia is classically seen following traumatic brain injuries and is often temporally graded, such that larger or more severe lesions to mesial temporal structures result in more chronologically extensive retrograde amnesia (i.e., with patients unable to recall events covering a greater number of past years [53]). Ictal memory disturbances 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. Finally, the combination of anterograde and retrograde amnesia has been termed *global* amnesia.

Amnestic Status Epilepticus

Vuilleumier and colleagues provided the most unequivocal description of an isolated memory disturbance resulting from nonconvulsive status epilepticus (NCSE) [54]. A 41-year-old, previously healthy woman was found trying to enter her former house where she had not lived for three years. 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 for time, and globally 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. Her forward digit span was 6, and from a 10-word list she recalled four words on the first two attempts and six words on the third attempt. She recalled only one word after a 3-minute delay. The only other finding on examination was occasional rhythmic eye blinking. An EEG showed continuous generalized epileptic activity with rhythmic spikes at 3.5–4 Hz. Within 4 min of the administration of an intravenous bolus of 1 mg clonazepam, this epileptiform pattern 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. The episode appeared to last 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 following 6 months of follow-up.

Lee and colleagues described the case of a young otherwise healthy woman who presented with the acute onset of amnesia [55]. She had limited recollection of the events of the preceding four months (retrograde amnesia), and examination showed normal working memory but with failure to recall any of three words or three hidden objects after a five-minute 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 ASDs led

to the complete cessation of epileptiform discharges and was followed by complete recovery of her memory, except for the events that transpired during the course of her illness. The duration of her amnestic episode was 12 days. While 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 post-ictal 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 due to status epilepticus.

A similar case of fluctuating memory loss was described by Dong and colleagues, where repeated scalp EEGs identified "nonspecific intermingled slow activity" only. An FDG-PET (fluorodeoxyglucose positron emission tomography) imaging identified hypermetabolic foci in temporal regions bilaterally (right > left), prompting an ASD trial, which improved both memory function and the PET findings [56]. These case reports are of interest as they establish the possibility that an isolated memory disturbance may (rarely) be the sole manifestation of NCSE, which may, as in the first case above, be associated with widespread electroencephalographic changes.

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 (with other semiologies, typically temporal lobe seizures), who had other symptoms suggestive of focal seizure activity preceding or during the amnestic attack and who responded to treatment with ASDs. For example, in the study by Zeman and colleagues [57], a rather strict definition of transient epileptic amnesia (TEA) was adopted (and consistently applied to subsequent studies), requiring (1) a history of recurrent witnessed episodes of transient amnesia, during which (2) cognitive functions other than memory were 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 co-occurrence of other seizure types or a clear-cut response to ASDs). The data from these reports are summarized in Table 21.3 [58–72], which includes representative data from 34 patients with TEA (see also Palmini and colleagues [73] and Mosbah and colleagues [74] for other case series). Anterograde amnesia was present in all but one patient, and most patients displayed a combination of anterograde and retrograde amnesia. Attacks were recurrent in all but two patients and varied from 2–3 per week to 1 per year. The duration of attacks varied widely, and in the vast majority of patients, attack frequently either markedly reduced or ceased completely following the initiation of ASD therapy.

Consistent with a central role for the hippocampus in the formation and recall of episodic memory, ictal activity in attacks of TEA are believed to be largely restricted to memory-serving mesial temporal lobe structures [49]. While this has not been demonstrated unequivocally with intracranial EEG, this hypothesis is supported by the fact that semiologic features of TEA attacks resemble the chronic impairment of memory function seen in patients with bilateral hippocampal lesions (such as following theophyiline-induced status epilepticus [50]). Second, subtle volumetric reductions in mesiotemporal structures have been documented in patients with TEA, which correlate in magnitude with interictal measures of anterograde memory [75, 76]. Finally, a single case report describes a patient with medically refractory TEA (and other associated complex partial seizures) who achieved a complete remission following a right anterior temporal amygdalohippocampectomy [77].

In addition to TGA (*transient global amnesia*, see below), TEA has also been diagnosed in patients with suspected mild cognitive impairment (MCI). In a cohort of 76 patients with MCI, a routine EEG using high-density EEG electrodes identified frontotemporal epileptiform discharges in three patients. In retrospect, all three patients displayed both mild persistent memory deficits and clearly paroxysmal episodes of mixed amnesia. The initiation of ASD therapy in all three patients led to a resolution of episodic amnestic events [78]. Similar findings have been reported in two other small case series [79, 80], indicating that TEA should remain high on the differential diagnosis for classically demented patients who display episodic deteriorations in orientation such as wandering behavior.

Transient Global Amnesia

Tranisent global amnesia (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 24 h. The syndrome is most common in patients between the ages of 50 and 70 years, and the affected individual is usually able to continue with complex activities but tends to ask the same questions repetitively despite their being answered appropriately. TEA and TGA bear a number of phenotypic resemblances. Each may be characterized by short-lived periods of global amnesia. In both, patients are able to continue with otherwise complex activities, due in large part to the amnesia occurring as an isolated cognitive deficit. How then can the two be differentiated? In Hodges and

Table 21.3 Ictal amnesia

References	Amnesia	Repetitive questioning	Associated features	Recurrence	Duration	EEG	Response to ASDs
Lou [58]	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 and Bennett [59]	A + R	No	Slow speech and movement	None	4 h	Bitemporal spikes (I and I-i)	Not stated
Gilbert [60]	A + R	Yes	None	None	9 h	Bitemporal short sharp spikes (I-i)	Not stated
Dugan et al. [61]	A	Yes	None	3 episodes	3 h	Bitemporal spikes (I, but not I-i)	Yes
Deisenhammer [62]	A + R	Yes	Headache; frightened and tearful	3 episodes	10 min	Mid-anterior temporal spikes (I and I-i)	Yes
Pritchard et al. [63]							
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 et al. [64–66]							
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 et al. [67]	A > R	Yes	Loss of contact; automatisms	8–10 episodes	minutes–hours	Temporal slowing; small sharp spikes (I-i)	Yes
Meador et al. [68]	A or R	No	Micropsia briefly; loss of contact	2 episodes	10–15 min	Bilateral epileptiform discharges (I-i)	Yes

(continued)

Table 21.3 (continued)

References	Amnesia	Repetitive questioning	Associated features	Recurrence	Duration	EEG	Response to ASDs
Kopelman et al. [69]	A	Yes	Fist clenching on two occasions	9 episodes	30–60 min	Temporal sharp and slow wave complexes	Yes
Kapur [70]							
Case 1	A + R	Yes	Lip smacking and gulping	35 attacks	minutes–hours	L temporal slowing (I-i)	Yes
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 of spike and slow waves (I-i)	Yes
Case 4	R	No	Preceding period of "confusion"	2 episodes	minutes	Not reported	Yes
Zeman et al. [71]							
Cases 1–10	A + R	Yes	Olfactory hallucinations; *déjà vu*; vertigo	2–30 (mean 9)	<1 h (n = 6) hours–days (n = 2)	Epileptiform activity (I-i) in 4 patients	Yes
Sugiyama et al. [72]	A + R	Yes	Brief unresponsive period	2	30 min	Right frontotemporal spikes	Yes

A anterograde, *R* retrograde, *I* ictal EEG, *I-i* interictal EEG, *R* right, *L* left, *ASDs* antiseizure drugs

Warlow's [81] study of 153 patients with acute transient memory loss, those who went on to develop epilepsy subsequently (i.e., recurrent attacks of TEA associated with other temporal lobe seizures) had a greater number of attacks at presentation and also, attacks of shorter duration. Other epileptic features (including other signs of temporal lobe seizure activity, such as automatisms or blank staring) are usually absent in episodes of TGA [82]. Without clear distinguishing historical features, providing prognostic information to patients and their families about recurrence risk is challenging. Indeed, recurrent epileptic attacks of amnesia (responsive to ASDs) can emerge after a single episode of transient global amnesia, as illustrated in the case described by Sugiyama and colleagues [72].

The etiology of TGA is unknown and likely variable across patients. Focal ischemia in the hippocampus has been proposed as a possible etiology, and in many but not all cases, diffusion weighted magnetic resonance imaging may show a punctate focus of cerebral ischemia in the hippocampus, typically in CA1. Such restricted diffusion is likely not the result of a traditional *cerebrovascular* insult (such as embolic stroke or lipohyalinosis) but rather, may reflect the vulnerability of this particular brain region to ischemic changes that may occur in the setting of otherwise subtle metabolic derangements [49]. Punctate foci of restricted diffusion may also reflect the effects of a prolonged highly focal hippocampal seizure. Indeed, focal epileptic activity or variant migraine, or both, have been proposed as possible etiologic underpinnings but have been more difficult to substantiate due to limited biomarkers and also likely due to the limited recurrence of the syndrome [49]. A number of TGA cases also demonstrate a clear emotional trigger, including bad news, heated arguments, or sexual intercourse [49], supporting the possibility that TGA attacks are a provoked response to an acute insult, either physiologic or psychologic, perhaps related to a surge in circulating corticosterone levels [82] which can be detrimental to hippocampal function [83].

Conclusion

It should be clear that an epileptic etiology of transient memory disturbances cannot be discerned on the basis of the amnestic phenotype alone. 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 previous similar episodes is also extremely helpful. Finally, a careful history and examination may disclose subtle ictal manifestations such as a history of *déjà vu*, olfactory hallucinations, rising

epigastric sensations, automatisms, brief periods of loss of contact, or combinations of these. Under appropriate circumstances, an empiric trial of ASDs may be appropriate, and a beneficial response validates the suspicion that the events were epileptic in origin. Ancillary measures of focally altered metabolism, such as FDG-PET, may be useful during symptomatic periods.

Ictal Psychosis

Introduction

Psychosis, defined as the occurrence of hallucinations or delusions that are associated with a loss of contact with reality, can occur in the context of epilepsy, seizures, or status epilepticus. Conceptually, it is helpful to recognize three distinct entities—*ictal*, *post-ictal,* and *interictal* psychosis. Interictal psychosis (also termed *chronic interictal psychosis*) refers to psychotic symptoms that occur in patients with epilepsy that are *not* acutely related to seizures. Interictal psychosis has been the subject of many studies, with most investigators describing a syndrome reminiscent of schizophrenia [84–87]. The underlying pathophysiology remains unclear (as with schizophrenia itself) and the treatment of interictal psychosis parallels the treatment of schizophrenia, encompassing a synergy of psychopharmacologic and behavioral interventions that address both positive (hallucinations and delusions) and negative (anhedonia, isolation, and affective blunting) symptoms [88], as well as appropriate treatment of the underlying or comorbid epilepsy [89]. Since some antipsychotic/neuroleptic medications are themselves associated with a lowered seizure threshold (e.g., clozapine, chlorpromazine), balancing the burden of psychotic and epileptic symptoms can be challenging [90].

Distinct from *interictal* psychosis are *ictal* psychosis (where psychotic symptoms are the direct manifestation of seizures), and *post-ictal* psychosis, in which psychotic symptoms immediately follow seizures. All three phenomena are seen primarily in patients with temporal lobe epilepsy [90, 91]. Psychosis can also occur *de novo* as a postoperative complication following a temporal lobectomy for drug refractory temporal lobe epilepsy, further implicating the temporal lobes and their associated limbic networks as being critical neuroanatomic substrates for the expression of psychotic symptoms [90]. Finally, a fourth and distinct syndrome has been labeled "alternating psychosis" or "forced normalization", in which psychotic symptoms are associated with the iatrogenic suppression of epileptic activity [88]. In some instances, depression may dominate the clinical picture together with nonepileptic seizures [92, 93]. It remains unknown whether these psychiatric symptoms are etiologically related to an idiosyncratic side effect of a specific ASD or are indeed a maladaptive compensation to the loss of previous epileptiform activity.

Ictal Psychosis

There have been relatively few descriptions of true ictal psychosis in the literature where *both* epileptiform EEG changes *and* psychotic symptoms cease with the administration of an ASD [94–96]. In the largest published series, Tucker and colleagues described 20 patients admitted to a psychiatric service because of behavioral disturbances and subsequently found to have temporal lobe epilepsy [97]. The clinical details of these and other patients are summarized in Table 21.4 [94, 95, 98–100]. Only six patients had a known history of epilepsy. All patients reported "spells" characterized by losing track of time, staring, feeling dazed, or being in a dream-like 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%) 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 did not clearly represent potentially epileptogenic activity. On the other hand, the episodic nature of these symptoms with many of the associated clinical features typical of temporal lobe complex partial seizures, as well as the response (partial or complete) to ASDs, provide strong circumstantial evidence that these patients had underlying epilepsy.

Post-ictal Psychosis

Post-ictal psychosis has been the subject of greater study and is probably not uncommon [101]. There are, however, relatively few detailed reports of its clinical phenomenology [102–105]. Psychosis may develop following either primary generalized [103, 104] or complex partial seizures [102]. In the majority of patients there is a clear history of either a prolonged seizure or increased seizure frequency prior to the onset of psychosis [106]. In some instances it may be precipitated by abrupt withdrawal or a change in ASD therapy [107]. Full recovery from the seizures and post-ictal

Table 21.4 Ictal psychosis

References	Clinical symptoms	EEG	Response to treatment
Takeda et al. [94]	Mood lability; A hallucinations; restless, anxious, fearful; estranged from the outside world	L amyg rhyth spikes	Complete response
Tucker et al. [98]			
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	Rhyth slowing R + L	Partial response
Case 12	Auditory illusions; automatisms	Nonspecific	Complete response
Case 13	Polyopia; panic attacks; suicidal ideation; forced thoughts; spells with automatisms	R + L spikes	Complete response
Case 14	Staring spells; episodic dyscontrol; paranoid and suicidal ideation; A and V hallucinations	Nonspecific	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 and suicidality; automatic and bizarre behavior	Nonspecific	No response
Case 20	Episodic dyscontrol and suicidality; A, V, and O hallucinations; mood lability; *déjà vu*	L S&SW	Partial response

(continued)

Table 21.4 (continued)

References	Clinical symptoms	EEG	Response to treatment
Tisher et al. [95]	Episodic command auditory hallucinations, usually but not always ego-dystonic	Paroxysmal activity	Not stated
Kim et al. [99]	V hallucinations, out of body experiences, panic attacks with choking	R rhythmic delta activity	Complete response
Praharaj et al. [100]	Abulia, muttering and smiling, assaultive/abusive behavior toward spouse	Desynchronized	Complete response

EEGs are interictal 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

Table 21.5 Post-ictal 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

confusion are observed in most patients, with psychosis developing after a lucid interval lasting anywhere from a few hours [104–106] to one month [102]. Paranoid delusions (that are typically, but not always, poorly systematized) are common [102–105], as are symptoms of affective disorders [102, 103]. Hallucinations are most frequently visual, less often auditory, and rarely tactile or olfactory [102, 103]. Multimodal hallucinations occur in a significant minority of patients. In the end, post-ictal 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 21.5.

Conclusion

Psychotic symptoms often occur in a close temporal relationship to seizures, particularly those arising from temporal regions. For reasons that in part relate to the difficulties of studying the electrographic correlates of episodic psychosis, it is difficult to clearly distinguish ictal from post-ictal psychosis. Those with ictal or post-ictal 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 reasonable to consider focal status epilepticus in the differential diagnosis. Universal screening of all cases of new onset psychosis with a routine EEG, however, may not be cost effective [107]. Similarly, given the often-transient nature of epileptiform abnormalities, long-term video EEG monitoring (at least 24 h) may be more suitable in select candidates.

Other Focal Manifestations of Status Epilepticus: Fear, Panic, and Depression

If focal seizures or status epilepticus can produce a selective impairment in highly circumscribed cognitive domains (such as language or the formation of episodic memories), then can focal seizures produce a selective impairment in emotional behavior? There have been several reports that document the presence of fear or panic as the sole manifestation of status epilepticus or frequent seizures [108–115] with simultaneous scalp (or in certain cases, depth) EEG recordings showing epileptiform activity in a variety of regions, including frontal, cingulate, occipital, and parietotemporal, arguing for the presence of a distributed network of brain regions that are involved in the expression of ictal fear or panic [116]. Importantly, many of these patients had been misdiagnosed

as having primary psychiatric disturbances (such as panic attacks) or psychogenic nonepileptic seizures, and an underlying epileptic etiology was often suspected only after a generalized convulsion was observed.

Mood and anxiety disorders together account for a significant proportion of the burden of psychiatric symptoms experienced by patients with epilepsy [117, 118], and the complex *bidirectional* interrelationships between epilepsy and mood and anxiety disorders have been extensively reviewed elsewhere [93, 119, 120]. While depressive symptoms are common in interictal periods, to our knowledge, there has been only one unequivocal report of depression as the sole manifestation of status epilepticus. Dimitriadis and colleagues [121] reported a case of an adult man who had recently been initiated on ASDs after a first generalized convulsion. Approximately one month later, his spouse noticed a 2–3-day period of sudden and noticeable change in behavior characterized primarily by depressed mood, loss of interest, fatigue, self-blame, and suicidal thoughts. An EEG in this acute setting showed left temporal status epilepticus, and both his symptoms and electrographic findings resolved with the administration of a benzodiazepine. This case exemplifies the need for the consideration of an epileptic etiology to new onset and seemingly unexplained emotional symptoms. Indeed, the combination of an unprovoked seizure associated with a psychiatric prodrome should raise suspicion for an underlying paraneoplastic autoimmune encephalitis [122] and prompt the early institution of continuous video EEG monitoring and ASD treatment [123].

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. In particular, new onset aphasia that may be transient is often first 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 this way. Similarly, a first episode of transient amnesia may be related to ischemia, but both transient global amnesia and transient epileptic amnesia remain on the differential diagnosis. These two disorders may be distinguished by the history of prior similar attacks and by the duration of the individual episodes. The distinction between the two has important implications for prognosis and treatment. Finally, psychosis, panic, fear, or depression symptoms are rarely the sole manifestation of epileptic activity, and there have been several cases where such patients are inappropriately treated with psychopharmacologic agents prior to considering an epileptic etiology.

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. Nevertheless, it is important to remember the limitations of surface EEG recordings for ictal and interictal discharges arising from mesial temporal lobe structures as well as other deeper brain regions, such as the cingulate or the orbitofrontal cortex. In these instances, semiquantitative indices of changes in focal cerebral metabolism, such as FDG-PET or SPECT, may provide additional diagnostic clues. Ultimately, an empiric trial of ASD therapy may be the only clue to an underlying epileptic etiology, and the cessation of focal cognitive changes may or may not occur immediately.

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Initial Treatment of Nonconvulsive Status Epilepticus

22

Aidan Neligan and Matthew C. Walker

Introduction

The primary issue in any discussion of the management and treatment of nonconvulsive status epilepticus (NCSE) is its heterogeneity. NCSE can take many different forms, and there is a multitude of underlying etiologies. These conditions are similarly categorized because they share the presentation of impairment of consciousness, behavioral changes, or both due to on-going seizure activity in the absence of significant motor activity, but in terms of prognosis and, we would argue, treatment approaches, they are very different conditions.

The International League Against Epilepsy (ILAE) has recently published guidelines on the definition and classification of status epilepticus (SE) [1], in which SE can be subdivided by semiology based on the presence (convulsive status epilepticus (CSE)) or absence (NCSE) of prominent motor symptoms. Both CSE and NCSE can then be further subdivided by the degree (qualitative or quantitative) of impairment of consciousness. The central conceptual advance of this paper, however, is the proposal of distinct time points (operational dimensions): t_1 (the time point at which a prolonged epileptic event should be considered SE and treatment initiated—which the Task Force proposed should be after 5 min for CSE); and, t_2 (the time point after which the potential for irreversible cerebral damage is likely to occur with on-going seizure, which the Task Force suggested should be 30 min for CSE). The authors provided supportive evidence for t_1 and t_2 in CSE based on clinical and experimental data that indicate that the longer convulsive seizures persist, the higher the risk of morbidity and mortality and the less effective the treatment options [2–5].

Whether or not such dimensions should be applied to, or indeed are appropriate for, NCSE or for which forms of NCSE, is unclear. Moreover, while there is an abundance of expert opinions and reviews on the management and treatment of NCSE (for example, Walker 2009 [6]; Meierkord and Holtkamp 2007 [7]; Pang and Drislane 2012 [8]; Ferguson and colleagues 2013 [9]; Fernández-Torre and colleagues 2015 [10]; and Sutter and colleagues 2016 [11]), evidence for treatment is largely derived from treatment trials for generalized CSE (which are themselves limited) or small case series. Consequently, any review of the treatment of the NCSE risks being biased, prescriptive, and potentially repetitive.

Definition, Epidemiology, Subtypes

In this chapter, we define NCSE as a state of prolonged seizure activity with a resultant change in behavior or level of consciousness [12]. Giving an accurate estimate for the incidence of NCSE is difficult precisely because of the heterogeneity of its presentation and the need for electroencephalography (EEG) recording to confirm the diagnosis. Nevertheless, the increasing availability of EEG, particularly in intensive care units (ICUs), has led to increased recognition of the possibility of NCSE in critically ill patients, now comprising one of the major groups in whom NCSE occurs. Indeed, in a study of 236 comatose patients in the ICU, aged between 1 month and 87 years, with no overt clinical signs of seizure activity and in whom a diagnosis of seizures was not suspected, 19 patients (8%) were found to be in NCSE, underscoring the potential scale of the underdiagnosis [13]. While once considered rare, it is now recognized that NCSE may constitute up to a third of cases of SE [14], with the proportion increasing if "SE in coma" is included. An estimate of 10–20 cases of NCSE per 100,000 person years has been suggested as the incidence rate [14].

Given the accepted heterogeneity of NCSE, any discussion on the evidence for the efficacy or indeed, need, for intervention should be based on the individual subtypes of NCSE. This of course has the inevitable disadvantage of further limiting the available data.

A. Neligan · M.C. Walker (✉)
Institute of Neurology, National Hospital for Neurology and Neurosurgery, University College London, Queen Square, London, WC1N 3BGUK
e-mail: m.walker@ucl.ac.uk

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Table 22.1 Types of nonconvulsive status epilepticus

Absence status epilepticus (ASE)
Typical absence status epilepticus (in the IGEs) de novo absence status epilepticus (in the elderly) Atypical absence status epilepticus
Simple partial status epilepticus (SPSE)
Complex partial status epilepticus (CPSE)
Complex partial status epilepticus in people with epilepsy Complex partial status epilepticus occurring *de novo*
Nonconvulsive status epilepticus in coma
"Subtle status epilepticus" (evolving from overt GCSE) Nonconvulsive status epilepticus in comatose patients with subtle signs of seizure activity Incidental finding of nonconvulsive status epilepticus on EEG in critically ill patients

IGE idiopathic generalized epilepsy, *GCSE* generalized convulsive status epilepticus, *EEG* electroencephalogram

NCSE can be subdivided according to whether there is a prior diagnosis of epilepsy and whether the patient is ambulatory or comatose, as these factors appear to have a major influence on prognosis [6, 10, 15–17]. Broadly speaking, NCSE consists of simple partial status epilepticus (SPSE) or *aura continua*, typical absence status epilepticus (TAS), complex partial status epilepticus (CPSE), and NCSE in coma. All of these can occur de novo or in the context of prior epilepsy. NCSE in coma can be further subdivided into NCSE in the critically ill and NCSE following CSE (Table 22.1).

Neuronal Damage in NCSE—Do We Need to Treat?

There is abundant evidence from clinical studies and animal models as to the deleterious effect of on-going seizure activity in the context of CSE [3, 5, 18, 19], necessitating prompt intervention and treatment [1]. In contrast, there is much debate concerning the evidence for neuronal damage in NCSE [15, 16]. Moreover, the decision to treat is based on the risk–benefit ratio, whereby the efficacy of an intervention has been firmly established and the benefits outweigh any potential risks or the risk of nonintervention [9]. Ultimately, the decision whether treatment is initiated or not is predicated on whether a reliably effective treatment exists and whether failure to treat results in on-going deleterious cerebral effects and consequently increased morbidity and mortality. We will examine the evidence for efficacy and necessity of treatment for the four main individual subtypes of NCSE, namely typical absence status epilepticus, simple partial status epilepticus, CPSE, and NCSE in coma. Lastly, we will address the issue of use of anesthesia in NCSE.

Absence Status Epilepticus

Typical absence status epilepticus (ASE) usually occurs in children or adolescents with an idiopathic generalized epilepsy (IGE) or those with a history of an IGE in childhood; it can, however, sometimes occur de novo or as a late presentation of IGE in the elderly [20]. It manifests as varying degrees of alteration in mental status or behavior. This is associated with the classical EEG pattern of large symmetrical bilateral synchronous 2.5–3 Hz spike and wave discharges, although this pattern may become discontinuous the longer it persists. The natural history of typical ASE is a duration of several hours, with spontaneous cessation, although it can persist several days, ending in a generalized convulsive seizure in up to a third of cases. Typical absence status is often precipitated by anti-seizure drug (ASD) withdrawal, or ASD non-adherence—with re-instatement of therapy a significant component of management. Typical ASE can also be precipitated by the use of inappropriate ASDs such as carbamazepine or phenytoin [21].

There are several genetic models of absence epilepsy and seizures in rodents, such as the homozygous tottering (Cacana1atg) model and the homozygous lethargic (Cacnab41h) model, each manifesting with spontaneous frequent absence seizures resembling continuous ASE, in addition to the pentylenetetrazole (PTZ) model of pharmacologically induced absence seizures [22–24]. Importantly, none of these models exhibits neuropathological sequelae [24]. Similarly, there appears to be no clinical evidence of increased morbidity or mortality associated with ASE in children [25–27], nor indeed in de novo ASE in later life [28], which can often occur as a consequence of benzodiazepine withdrawal [29]. Indeed, continuous generalized 2.5–3.5 Hz spike wave discharges were identified on EEG in one 8-year-old girl followed up over 9 years without neurocognitive sequelae [30].

Acute treatment of ASE is, therefore, mostly aimed at preventing injury due to the altered conscious state or the occurrence of a convulsion. The consensus is that ASE responds rapidly to treatment with oral or IV benzodiazepines [6, 7, 9, 27] particularly clonazepam [27] (Table 22.2 [10, 31]), or IV valproate or oral acetazolamide when benzodiazepines are contraindicated. Moreover, successful management requires identification and correction of and avoidance of potential precipitating factors, if possible, such as acute systemic infections, psychotropic drugs, use of inappropriate ASDs, or alcohol withdrawal [26, 27, 29, 32]. Interestingly, episodes of ASE may be triggered by use of inappropriate ASDs such as carbamazepine and phenytoin which may render standard treatment [benzodiazepines (BZDs) or valproic acid (VPA)] ineffective due to a paradoxical effect of the inappropriate ASD, underscoring the risk of iatrogenic exacerbation of ASE [21, 33]. For people

Table 22.2 Suggested treatment regimens for nonconvulsive status epilepticus [10, 31]

Type of NCSE	Suggested treatment
Typical absence status epilepticus	PO or IV BZD, VPA[a]
de novo absence status epilepticus	PO or IV BZD, VPA
Atypical absence status epilepticus	PO or IV BZD, VPA, PHB
Simple partial status epilepticus	PO or IV BZD, VPA, PHT or LEV
Complex partial status epilepticus	PO or IV BZD, PHT, VPA or LEV IV AD only with caution and in people with an otherwise good prognosis
Subtle status epilepticus	PO or IV BZD, PHT, VPA or LEV. IV ADs (PRO, MDZ or PHB). Other options TPM, LCM, or KTM amongst others[b]
Nonconvulsive status epilepticus in coma with subtle signs of seizure activity	As above, but less aggressive treatment advocated
Nonconvulsive status epilepticus on EEG in critically ill patients without signs of seizure activity	Treatment of NCSE is unclear but can worsen prognosis and should be used cautiously

[a]All suggested treatment regimens include identification and correction of potential precipitants when possible
[b]Modified from Shorvon and Ferlisi [31]
AD anesthetic drugs, *BZD* benzodiazepines, *IV* intravenous, *KTM* ketamine, *LEV* levetiracetam, *MDZ* midazolam, *PHB* phenobarbital, *PHT* phenytoin, *PRO* propofol, *TOP* topiramate, *VPA* valproic acid

with IGE prone to recurrent episodes of typical ASE, long-term therapy appears to be efficacious in significantly reducing or preventing further attacks [34]. The elderly with NCSE de novo rarely require longer term treatment.

Atypical ASE, which typically occurs in the context of the epileptic encephalopathies such as Lennox–Gastaut syndrome, can be quite refractory to non-anesthetic drugs, which nevertheless remain the preferred method of treatment. Moreover, treatment with BZDs needs to be employed cautiously, as this may precipitate tonic SE in some of these patients [35].

Compared to typical ASE, impairment of consciousness is reputedly more severe in atypical ASE, but the EEG may not differentiate the two. Treatment with second-line agents such as VPA or phenobarbital may be necessary at times (Table 22.2). Anesthesia should be avoided as treatment for patients with ASE (see below).

Simple Partial Status Epilepticus

Simple partial status epilepticus (SPSE) or *aura continua* is considered a rare form of SE, but because it lacks motor features or impairment of consciousness, it may go unrecognized. SPSE arises as a result of seizure activity involving a focal area of cortex, with diverse clinical presentations including aphasia, visual or auditory hallucinations, altered perception, transient visual loss, and episodes of fear. Similarly, SPSE may take the form of focal motor seizures, aversive eye movements, transient paralysis contralateral to the epileptic focus, or focal myoclonic jerks with or without impairment of consciousness (*epilepsia partialis continua* [EPC]) lasting days to months—which may be highly refractory to treatment [36]. In the largest reported series, among 47 people with new onset SPSE identified retrospectively over a 5-year period in the Netherlands, all but one (with aphasia) had somatomotor SPSE; 20 had EPC. Just over half (27) had a previous diagnosis of epilepsy, although the SPSE was caused by a new neurologic diagnosis in six. Of those without a prior diagnosis of epilepsy, cerebrovascular disease was the most common etiology of SPSE, in 14 patients. Overall, four patients died (all due to acute cerebrovascular disease) and ten had associated morbidity, only one case of which was felt to be attributable to the SPSE. In general, SPSE appears to be associated with low mortality and morbidity, almost always caused primarily by the underlying etiology. Treatment, first with oral or IV BZDs (e.g. clonazepam) followed, if necessary, by IV phenytoin, is usually effective (Table 2). Anesthesia should, if possible, be avoided in patients with SPSE (see below).

Complex Partial Status Epilepticus

Complex partial status epilepticus (CPSE) is in contrast probably the most frequent subtype of NCSE, reportedly accounting for up to 40% of cases of SE overall [12, 37]. The presentation of CPSE can be very heterogeneous and primarily determined by the origin of the epileptic focus. Fluctuating consciousness, with or without amnesia is the typical presentation, but altered consciousness may not occur in CPSE with a unilateral frontal lobe focus [38]. It can be difficult to distinguish CPSE from ASE, especially in the elderly with de novo ASE. Moreover, while CPSE needs to be differentiated from other forms of NCSE, it also needs to be distinguished from other causes of encephalopathy

(e.g., hepatic encephalopathy), prolonged post-ictal states, or primarily psychiatric behavioral changes. This is often not straightforward. EEG is not always helpful, as the changes on scalp EEG in CPSE can be relatively nonspecific, so the diagnosis of CPSE remains primarily an electro-clinical one. Nevertheless, strict electrographic criteria for the diagnosis of CPSE need to be employed [39, 40].

Similarly, response of the EEG to treatment, in particular with BZDs, cannot be used as a reliable diagnostic indicator of CPSE because some EEG abnormalities, such as the triphasic waves of hepatic encephalopathy, may also improve with BZDs [41]. Conversely lack of immediate clinical improvement should not exclude the diagnosis, as often the confusion of CPSE may be replaced by the confusion of the post-ictal state without any obvious change in clinical condition.

CPSE is considered the result of focal seizures spreading to involve bilateral cerebral structures, presenting with variable degrees of impairment of consciousness, with partial or complete amnesia, typically gradual in onset and often recurrent [42]. While originally referred to as "psychomotor status" arising from the temporal lobes, a depth electrode study of 87 people with complex partial seizures showed that of the eight who developed CPSE, all had extra-temporal CPSE, with frontal lobe origin definitely established in four [38].

In a prospective study of 10 patients identified with CPSE of frontal lobe origin, there was a significant delay in recognition and diagnosis of CPSE (mean time to diagnosis, 48 h). In the first type of frontal CPSE, seven patients presented with mood disturbances or affective disinhibition with subtle impairment of cognitive function, but without overt confusion [43]. This was associated with a unilateral frontal epileptiform ictal pattern, with normal background activity. In the second type of frontal CPSE, three patients presented with impaired consciousness with an EEG pattern of bilateral asymmetric frontal discharges on an abnormal background [43].

CPSE is clinically subdivided into (1) CPSE in patients with epilepsy and (2) CPSE de novo. This is in part based on the recognition that the prognosis of CPSE in those with a prior diagnosis of epilepsy is far better than that when CPSE occurs de novo in the context of an acute medical illness. Indeed, experimental evidence indicates that epilepsy and previous exposure to ASDs may be neuroprotective in CPSE [44].

Management of CPSE is controversial, with many authors advocating aggressive treatment. This is, in part, because animal models of CPSE can demonstrate severe neuronal damage [45]. Nevertheless, the mechanisms of seizure generation and propagation in animal models may not accurately reflect human CPSE [6]. Moreover, CPSE in humans is typically characterized by lower frequency discharges than those seen in animal models [46]. When animal models are reproduced using these lower frequency discharges, significantly less damage is produced than with the higher frequency discharges [47].

The clinical data from case series suggest a more favorable prognosis, particularly in people with CPSE in the context of previous epilepsy [42, 44]. In one series, 20 patients with CPSE were identified, of whom 17 had recurrent episodes, many of which were very prolonged, lasting a few days to a few months, with one case lasting 18 months [42]. In the 17 patients with recurrent episodes, nine experienced monthly episodes, with a range of one to six episodes per month. Despite the relative frequency and longevity of the episodes, none reported or demonstrated any neurocognitive sequelae. Five of the 17 patients underwent neuro-psychometric evaluation on more than one occasion over a period of two or more years, with no evidence of cognitive decline on formal testing.

This and other case series of CPSE [38, 42–44] suggest a relatively favorable prognosis in terms of neurocognitive sequelae. CPSE in those with prior epilepsy is typically responsive to oral BZDs such as clobazam or intravenous BZDs such as lorazepam or diazepam, although recurrence is not uncommon [42]. There may, however, be a delayed clinical response despite resolution of EEG features as the patient enters a post-ictal state. Consequently, EEG monitoring, when available, should be used to monitor the response to treatment. In the case of failure of response to oral or IV BZDs, IV ASDs can be considered [48, 49] (see Table 22.2). In the scenario where CPSE with prior epilepsy remains refractory to non-anesthetic agents, treatment escalation to IV anesthetics should only be considered with caution and on an individual basis. The paucity of clinical data for long-term neurocognitive consequences underlies the reticence of many neurologists to advocate escalation to IV anesthetic agents, given their association with morbidity and mortality [50].

De novo CPSE, occurring in the context of acute or progressive neurological conditions, is in contrast, often refractory to non-anesthetic agents. Prognosis, as with generalized CSE [51], is primarily determined by the underlying etiology, and successful management of the CPSE is contingent on the rapid recognition of the precipitating cause if possible. This is particularly true in the case of autoimmune encephalitis, such as anti-NMDA receptor encephalitis, which can result in CPSE resistant to standard ASDs and IV anesthetic agents, responding only after initiation of immunosuppressive therapy (IV steroids, IVIG, or plasma exchange) [52]. Because of the potential response of these conditions to immunosuppression, autoimmune encephalitis should be considered in all patients with SE and encephalitis of unknown origin, with early use of immunosuppression when there is a high clinical suspicion. In all these cases,

suitable examination and investigation should be performed to look for occult tumors (in particular ovarian, breast, and testes).

CPSE may be underdiagnosed in the ill elderly, and may contribute to confusion and the clinical state. In this instance, care needs to be taken with the use of intravenous BZDs, which can increase mortality. Generally, intravenous valproate or levetiracetam are preferred, as they have fewer adverse hemodynamic and respiratory effects. Anesthesia should, if possible, be avoided in patients with non-comatose CPSE (see below).

Nonconvulsive Status Epilepticus in Coma

Nonconvulsive status epilepticus in coma is considered the most severe subtype, with significant morbidity and mortality, and often poses the greatest diagnostic dilemma. It is also the area where there is the most controversy regarding treatment, with a current state of equipoise between aggressive intervention and nonintervention. NCSE in coma can be subdivided into three groups: (1) "subtle status epilepticus" as originally conceived by Treiman (1993), referring to the end stage or burnout of overt generalized CSE, whereby NCSE evolves from generalized convulsive status epilepticus (GCSE), typically in the context of partially or nontreated GCSE [53]; (2) electrographic SE with subtle clinical signs of seizure activity at presentation; and (3) electrographic SE found incidentally on EEG in the critically ill in coma.

Despite the significant morbidity and mortality associated with NCSE in coma there are few data to guide management or indeed, to inform us if intervention even impacts overall prognosis. "Subtle" NCSE is considered the most malignant form of NCSE, the management of which was studied in the Veteran's Affairs Status Epilepticus Study [54], where 570 patients with SE (375 with overt SE, and 175 with subtle SE) were randomized to one of four treatment arms: administration of lorazepam (0.1 mg/kg); diazepam (0.15 mg/kg) followed by phenytoin (18 mg/kg); phenobarbital (18 mg/kg); or phenytoin (18 mg/kg) alone. Successful cessation of SE was significantly better for overt SE compared to subtle SE in all four treatment arms: lorazepam (67% for overt SE, compared to 26.1% for subtle SE); phenobarbital (63% compared to 24.4%); diazepam and phenytoin (59.6% compared to 23.4%) and phenytoin (51% compared to 19.5%). While lorazepam was found superior to phenytoin in the treatment of overt SE ($p = 0.002$), no difference was found between any two treatment arms for the management of subtle SE ($p = 0.18$) [54].

Consequently, subtle SE should be treated as refractory generalized CSE, with IV anesthetic drugs as recommended by the European Federation of Neurological Societies (EFNS) [49] with administration of IV anesthetic drugs continued for a minimum or 24–48 h (Table 2). Such recommendations, however, are made with little to no supporting evidence in NCSE but are rather made as a pragmatic approach, as the few studies of third line treatments (IV anesthetic drugs) have been in the context of CSE, with generally poor outcomes [55, 56]. For the treatment of NCSE in coma in the critically ill, the use of anesthetic drugs is less controversial as many will already be under anesthesia. Whether the use of multiple ASDs and increased levels of anesthesia are justified is unclear. In most instances, the coma is not the result of the SE but usually due to some other devastating condition, and the risk of systemic complications from increasing the anesthetic dose needs to be considered. In most instances, the authors undertake trials of ASD treatment, but the evidence base for this approach is slight.

Anesthesia in NCSE

Although anesthesia will halt NCSE in most instances, IV anesthetic drugs themselves can be associated with significant morbidity and mortality, especially in the context of prolonged treatment of refractory SE such as is seen with propofol [57]. Indeed, it has been suggested that use of IV anesthetic drugs in refractory SE may also be associated with a higher risk of infections compared to treatment without IV anesthetic drugs (43% vs. 11%; $p < 0.0001$) and an increased relative risk of death (RR: 2.88; 95% CI 1.45–5.43) [58]. Interestingly, those with SPSE, CPSE, or ASE treated with IV anesthetic drugs demonstrated a trend toward a higher relative risk of death (RR: 3.28; 95% CI 0.79–13.67) compared to those with GCSE (RR 1.40; 95% CI 0.14–14.25) or NCSE (RR 1.69; 95% CI 0.71–3.69) treated with IV anesthetic drugs. It could be argued that this study did not adequately control for other factors, but a study of 467 patients with incident SE identified over a 7-year period did control for other factors (age, severity of SE, etc.) [59]. Fifty (10.7%) were treated with therapeutic coma. Overall, therapeutic coma was associated with poorer outcome, with a RR for new neurologic deficit, 6.86 (95% CI 2.84–16.56), and a higher risk of mortality (RR: 9.10, 95% CI 3.17–26.16), with the effect greater in patients with CPSE than in those with GCSE. Moreover, therapeutic coma was associated with a higher incidence of infection (odds ratio (OR) 3.81 (95% CI 1.66–8.75)) and longer hospital admission duration.

In contrast to these studies, in a retrospective single center study of 45 episodes of NCSE in 43 individuals identified over a 5-year period, IV anesthetic drugs were used in 31 episodes (69%) [60]. Of the 14 episodes treated with non-IV anesthetic drugs, 13 responded to treatment (two to IV BZD

alone; three to IV non-anesthetic ASDs, and eight to IV BZD followed by an IV non-anesthetic ASD). Of the 31 episodes of NCSE treated with IV anesthetic drugs, 24 (74%) responded to treatment, with patients receiving IV anesthetic drugs being younger, more likely to have an acute neurologic etiology, in coma, or already intubated prior to the diagnosis of NCSE being made. Overall, 12 (26.7%) presented with altered mental status (AMS), 20 (44.4%) with AMS and subtle motor signs, and 13 (28.9%) with 'subtle' SE (with AMS, or AMS with subtle motor signs following a generalized convulsion), with no significant differences in outcome between the groups. Further subdivision into clear NCSE subtypes other than subtle SE was not possible based on the data presented. Nevertheless, this study suggests that in carefully selected patients with NCSE, aggressive treatment up to and including IV anesthetic drugs may be appropriate.

In summary, we suggest that treatment of (1) subtle SE and (2) people with AMS with subtle motor signs, should be treated with IV ASDs up to and including IV anesthetic drugs, but this should be assessed on an individual basis. Moreover, treatment should be considered even in the context of prolonged duration of SE or time to SE diagnosis or treatment, as these may not be universal indicators of poor prognosis in NCSE [59, 61]. Their use in young people with acute neurologic insults and coma is less clear, but anecdotal evidence indicates that anesthesia can be effective. In the elderly with an acute neurologic cause, care needs to be taken, as the risk–benefit may well swing the other way with the complications of deep anesthesia outweighing the benefits. In ASE and SPSE, there is rarely any justification for such treatment, and anesthesia should, if possible, be avoided in those with CPSE.

Conclusions

Despite the limited data available to guide management of NCSE several recommendations can be made.

1. Consideration of the possibility and prompt diagnosis of NCSE is of paramount importance. This is particularly true in the case of subtle SE following GCSE and in AMS with subtle focal motor signs of seizure activity and underlies the importance of EEG monitoring in the first 48 h after GCSE.
2. ASE, SPSE, and CPSE are typically very responsive to oral or IV BZDs and IV ASDs. IV anesthetic drugs are rarely indicated and indeed should only be considered in select cases, as their use may, in some instances, worsen prognosis.
3. Perhaps even more so than with GCSE, the prognosis of NCSE is determined by the underlying etiology, with improvement being predicated on the nature of, identification of, and treatment of the underlying cause. Nevertheless, disentangling the relative contributions of the underlying etiology and the electrographic seizure activity to the observed cerebral dysfunction can be problematic.
4. There is currently a state of equipoise in how NCSE in coma should be managed or indeed how aggressive and persistent treatment should be. It would appear pragmatic that subtle SE evolving from GSCE should be treated as quickly as possible with IV anesthetic drugs, underlying the need for prompt recognition and diagnosis. This is also probably true for NCSE in coma with subtle motor signs, with the proviso that aggressive treatment with IV ASDs may be associated with worse outcomes.
5. Finally, we recommend clear delineation of the optimal management of NCSE in coma by means of randomized-controlled trials with clear subgroup analysis of the different subtypes of NCSE in coma. Such studies are very unlikely to happen given the lack of financial impetus for the pharmaceutical industry to help fund such undertakings. Consequently, the only way forward may be the pooling of multicenter data, and such initiatives are currently underway.

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Continuous EEG Monitoring for Status Epilepticus

23

Monica B. Dhakar and Lawrence J. Hirsch

Introduction

In recent years, there has been a rapid expansion in the utilization of continuous electroencephalography (C-EEG) in intensive care units (ICU). There are several indications for performing C-EEG in the intensive care setting [1], but the primary reason is for detection of nonconvulsive seizures (NCSz) and nonconvulsive status epilepticus (NCSE). NCSz, as the name suggests, refers to electrographic seizures with only subtle or no overt clinical signs (Fig. 23.1). NCSE has been variably defined as continuous or recurrent NCSz lasting more than 30 min without return to baseline, or NCSz lasting more than 50% of an EEG epoch [2]; and continuous or recurrent NCSz lasting more than 5 min [3]. Recently, an ILAE taskforce proposed a conceptual definition of status epilepticus (SE)—"*Status epilepticus is a condition resulting either from the failure of the mechanisms responsible for seizure termination or from the initiation of mechanisms which lead to abnormally prolonged seizures* (*after time point t1*). *It is a condition, which can have long-term consequences* (*after time point t2*), *including neuronal death, neuronal injury, and alteration of neuronal networks, depending on the type and duration of seizures*" [4]. For convulsive status epilepticus, time point t1 is estimated to be at 5 min, and t2 at 30 min. For focal SE with impairment of consciousness (one type of NCSE), the time points t1 and t2 are not well defined but were estimated as 10 and >60 min, respectively. Unified electrographic criteria for defining NCSz, based on expert opinion, have been published in recent reports (Table 23.1) [5–7].

In addition to diagnosing NCSz, prolonged monitoring is also necessary for monitoring the efficacy of treatment, especially when using anesthetics, and for guiding treatment for NCSzs and NCSE. The significance of NCSz and NCSE in terms of the effects on cognition, neurologic function, development of epilepsy, and other morbidity and mortality will be discussed in separate chapters. Suffice to say there is extensive and growing evidence (though no prospective randomized trials of treatment versus no treatment) that NCSE or a high burden of some types of NCSz is associated with worse neurologic outcomes, including in cognitive function and later epilepsy. This chapter reviews indications for continuous EEG in SE (particularly for NCSE) under different settings, duration of monitoring, diagnosis of NCSz, data review, and cost effectiveness of C-EEG in SE.

Yield of Continuous EEG

Several studies over the years have established clearly the necessity and, higher yield, of prolonged EEG monitoring in critically ill patients for diagnosing NCSz and NCSE [8, 9]. Routine EEGs, even when performed repeatedly, have a lower yield for detecting seizures, particularly NCSz [10]. In a retrospective study, the monthly rate of diagnosis of NCSz in ICU patients increased significantly after introduction of C-EEG [9]. In another study examining the utility of C-EEG in a neurological-neurosurgical ICU, all patients underwent a routine 30-min EEG prior to continuous video EEG monitoring, with a mean duration of 2.9 days (range 1–17 days). In the 105 patients, NCSz were detected in 26.7% with C-EEG, as compared to 11.4% with routine EEG [8].

Who Should Be Monitored with Continuous EEG?

The purpose of C-EEG in critically ill patients admitted to ICUs can be divided into two broad categories: (a) diagnosis of NCSz and NCSE and, (b) assessing the efficacy of treatment for seizures and SE.

M.B. Dhakar · L.J. Hirsch (✉)
Department of Neurology, Yale University School of Medicine, PO Box 208018New Haven, CT 06520-8018, USA
e-mail: lawrence.hirsch@yale.edu

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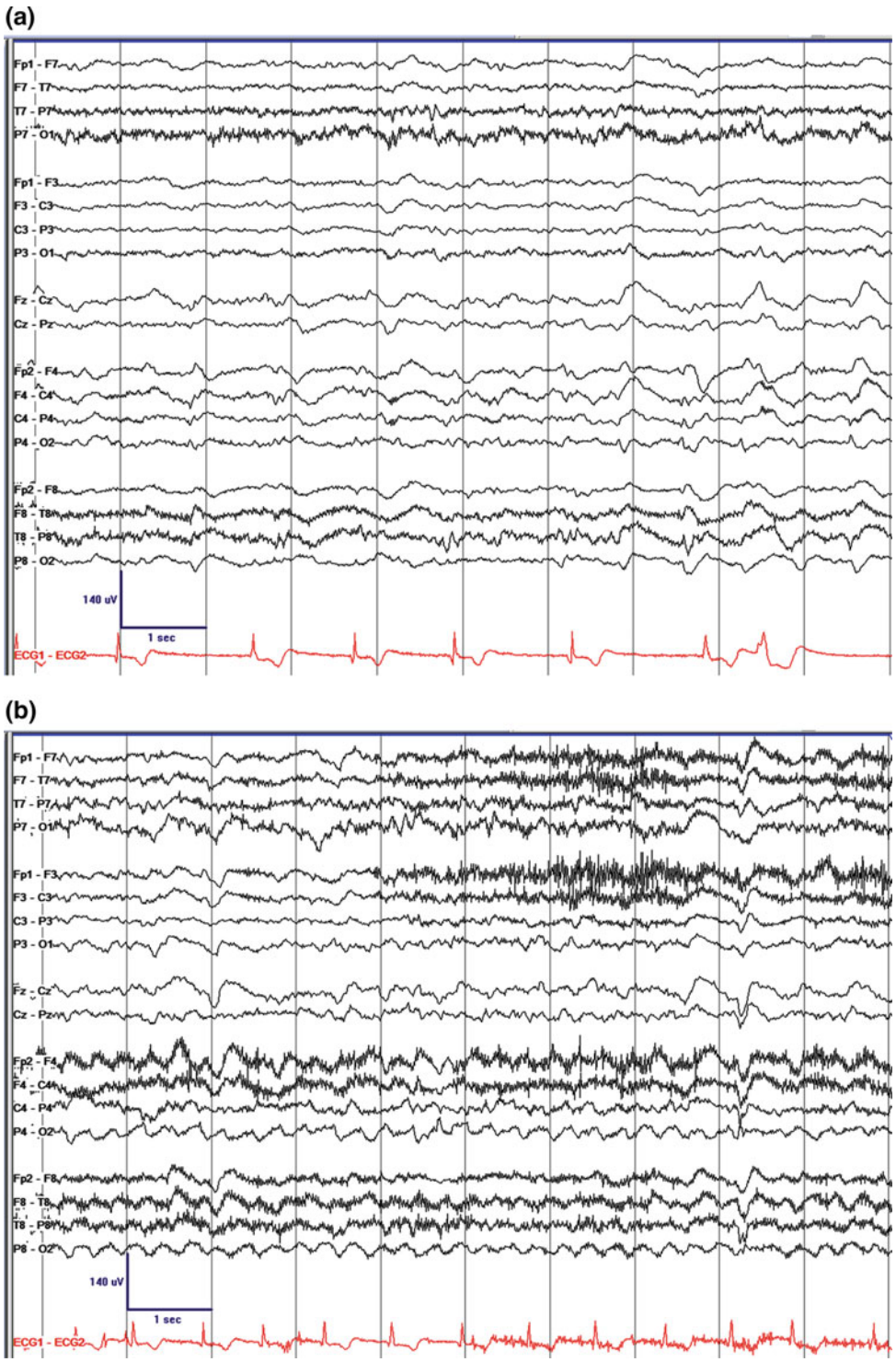


Fig. 23.1 The EEG of a nonconvulsive seizure. This is an EEG (settings: 7 uV; low-frequency filter: 1 Hz; high frequency filter: 70 Hz; and notch filter turned on), from an 87-year-old man with atrial fibrillation, on oral anticoagulant agent (apixaban) who was admitted with a traumatic right-sided subdural hematoma. He had 8 electrographic seizures in the first 7 h of EEG recording. Seizures began with 0.5 Hz delta slowing with periodic spikes in the right parieto-temporal region (**a**), which then increased gradually to 3 Hz and spread to the entire right hemisphere (**b** beginning 31 s after the end of **a**). This was associated with non-specific bilateral arm movements, none of which was recognized as a seizure at the bedside

Table 23.1 Criteria for the diagnosis of nonconvulsive status epilepticus

EDs > 2.5 Hz, *or*
EDs ≤ 2.5 Hz or rhythmic delta/theta activity (>0.5 Hz) AND one of the following:
EEG and clinical improvement after IV ASDs[a], *or*
Subtle clinical ictal phenomena during the EEG patterns mentioned above, *or*
Typical spatiotemporal evolution[b]

From Beniczky et al. [5] as modified from Kaplan [6], with permission
EDs; epileptiform discharges (spikes, poly spikes, sharp waves, sharp-and-slow-wave complexes)
IV ASDs; intravenous anti-seizure drugs
[a]If EEG improvement occurs without clinical improvement, or if fluctuation without definite evolution, this should be considered possible NCSE
[b]Incrementing onset (increase in voltage and change in frequency), or evolution in pattern (change in frequency >1 Hz or change in location), or decrementing termination (voltage or frequency)

Diagnosis of Nonconvulsive Seizures and Nonconvulsive Status Epilepticus

Nonconvulsive seizures (NCSz) are common among critically ill adult patients, but the percentage of patients with NCSz varies depending on the population studied. Across different studies performed in all ICUs, the prevalence of NCSz has been between 8 and 38% (Fig. 23.2) [11–35]. Although there is a high incidence of NCSz among patients with acute brain injury, even patients without neurologic injury but with serious systemic illness, especially sepsis, are at risk of NCSz. A single center retrospective study examined all comatose adult patients admitted to the ICU with no overt clinical signs of seizures; patients with prior clinical signs of seizures or SE were excluded [33]. Of 236 patients, 19 (8%) were found to have NCSE on a 30-min EEG. Subsequently, another large single center retrospective study utilized C-EEG for all patients of all ages with unexplained alternation in consciousness in hospital settings including both wards and ICU [16]. Of 570 patients, 110 (19%) had seizures, and 92% were exclusively nonconvulsive. About half of the NCSzs qualified as NCSE (59/105, 56%). There was a higher incidence of NCSzs among the patients admitted to the Neuro ICU (61%) compared to those in other settings. In this study, younger age, coma at onset, history of epilepsy, convulsive seizures prior to monitoring, and a burst suppression pattern on the EEG were independent predictors of NCSz [16]. Another study found that profound alteration of consciousness, oculomotor abnormalities, and previous risk factors for epilepsy were significantly associated with NCSE [36]. A recent prospective study from a single center found a similar rate of NCSz or NCSE—21% among all patients (n = 170) with altered mental status in a Neuro ICU [37]. They also found that subtle oral twitching and eye deviation was associated with 50% of cases of NCSz and NCSE (though this is likely to be due to selection bias related to who undergoes C-EEG). Among these patients, those with a previous history of epilepsy, brain tumors, and meningitis or encephalitis were at the highest risk of NCSz.

Convulsive Status Epilepticus. Often, patients remain obtunded after 'successful' treatment of convulsive status epilepticus (CSE), and it is difficult to differentiate a post ictal state from ongoing seizure activity. Studies have shown that even after successful treatment of CSE, approximately 43–48% of patients continue to have NCSz, and 14% have NCSE, on subsequent 24 h of C-EEG recording [6, 38]. Therefore, C-EEG is indicated in patients with convulsive seizures who do not show a clear improvement in alertness within 10 min of adequate treatment or who do not return to their functional baselines within 60 min of treatment with anti-seizure drugs (ASDs) [3, 39].

Acute Brain Injury. NCSz are a common occurrence in patients with acute neurologic injury, so C-EEG is indicated in all such patients with alteration of consciousness. Earlier studies from patients admitted to the Neuro ICU showed a high incidence of NCSz—up to 34%, with 76% of these being NCSE [40]. The variability in incidence of NCSz in these patients is partly attributable to methodologic variations in the nature of the studies, the underlying etiology, duration of monitoring, and possibly the use of ASDs and sedative medications.

Traumatic Brain Injury. All patients with traumatic brain injury (TBI) are at high risk of developing seizures, particularly those with depressed skull fractures, any intracranial bleeding, cortical contusions, or penetrating brain injuries. The estimated incidence of NCSz in TBI patients has varied from 3 to 53%. In 94 consecutive patients with moderate to severe TBI (defined as GCS of <12), seizures occurred in 22, and 52% of the seizures were exclusively nonconvulsive. The incidence of NCSE in the overall cohort was 6.3% [41]. The mean duration of monitoring was 7.5 (±4) days. The seizures occurred despite treatment with prophylactic ASDs. Thus, C-EEG is recommended for patients with moderate to severe TBI with alteration in consciousness, and in any TBI patients with penetrating injury or intracranial hemorrhage of any type.

Subarachnoid Hemorrhage. Patients with nontraumatic, aneurysmal subarachnoid hemorrhage (SAH) constitute another high-risk group for NCSz, with an incidence of NCSz of approximately 3–31% [42, 43]. Most of these studies were performed in poor-grade (more severe) SAH patients. Older age, female sex, higher Hunt and Hess grade of SAH, thick cisternal hemorrhage, need for ventriculostomy, cerebral edema on initial CT scan, and structural lesions were associated with a higher risk of NCSE [42, 43].

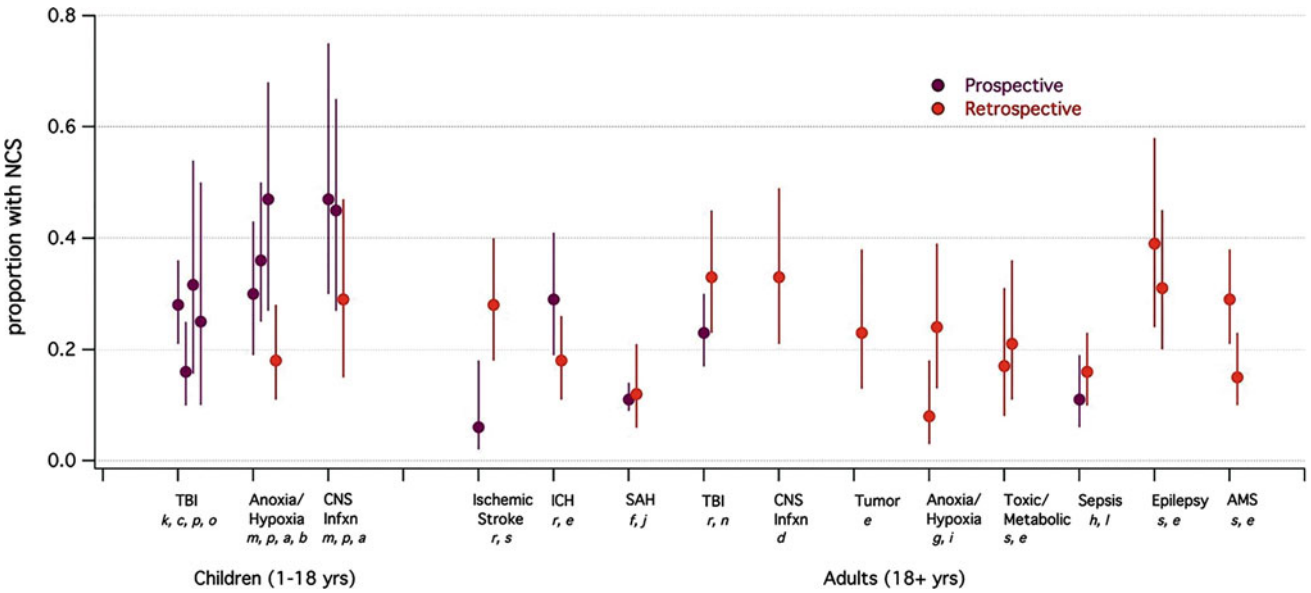


Fig. 23.2 Incidence of nonconvulsive seizures (NCS) in different populations of critically ill children and adults. The confidence intervals were not reported by the studies, but were calculated based on the number of subjects in the study and the proportion of patients in whom nonconvulsive seizures were detected. Data are derived from: *a* Abend et al. [12], *b* Abend et al. [13], *c* Arndt et al. [14], *d* Carrera et al. [15], *e* Claassen et al. [16], *f* Claassen et al. [17] *g* Crepeau et al. [18], *h* Gilmore et al. [19], *i* Mani et al. [20], *j* O'Connor et al. [21], *k* O'Neill et al. [22], *l* Oddo et al. [23], *m* Payne et al. [24], *n* Ronne-Engstrom and Winkler [25], *o* Schreiber et al. [26], *p* Topjian et al. [27], *q* Vespa et al. [28], *r* Vespa et al. [29], *s* Westover et al. [30]. Adapted from Osman et al. [11], with permission

Intracerebral Hemorrhage. Early clinical seizures are common in patients with nontraumatic intracerebral hemorrhage (ICH); the incidence ranges from 4 to 14% [44–46]. The incidence of NCSz is even higher when C-EEG is carried out on these patients. In 102 consecutive patients with ICH who underwent C-EEG monitoring, seizures occurred in 31%, over half of them (18/32) exclusively nonconvulsive, and 7% (7/102) qualified as NCSE [17]. These studies may have overestimated the occurrence of seizures as only the patients who underwent C-EEG monitoring were studied, rather than the total ICH population. Nevertheless, Vespa and colleagues reported the incidence of NCSz to be similarly high at 28% in patients with nontraumatic ICH, even when consecutive patients were studied without a selection bias [29]. Larger hematoma volume has been consistently demonstrated as highly associated with increased risk of seizures [17, 46]. One study also indicated that cortical involvement is predictive of increased occurrence of seizures [45]. The study by Vespa and colleagues confirmed the same findings, but another study found an association in univariate analysis only (possibly underpowered for multivariate analysis) [17, 29]. Periodic discharges occur with a higher frequency in patients with hemorrhages in close proximity (<1 mm) to the cortical surface [17], which in turn may increase the risk of seizures. Whether NCSz contribute to increasing cerebral edema and midline shift in patients with ICH remains unclear. Nonetheless, NCSz have consistently been an independent predictor of poor outcome [17, 42]. As with other critically ill populations, 56% of patients with NCSz had the first seizure detected within the first hour of C-EEG monitoring, and 94% within 48 h [17]. Based on these findings, C-EEG monitoring is recommended in all patients with ICH and impaired consciousness, particularly those with larger or expanding hematomas and those with hemorrhages in close proximity to cortex, including the insula (<1 mm).

Acute Ischemic Stroke. The prevalence of early seizures among patients with acute ischemic stroke (within 7 days) is considerably less compared to that with hemorrhagic stroke and has been estimated to be around 2.5% [47, 48]. (This population of solely ischemic stroke has not been studied extensively with C-EEG.) In a prospective study of 232 patients, of whom 177 had acute ischemic stroke, 4.3% had SE (10% being NCSE), all within the first 24 h of stroke onset [48]. The incidence was similar among ischemic and hemorrhagic stroke. Another cohort of 100 consecutive patients (91 with ischemic stroke and 9 with hemorrhagic stroke) who were admitted to a stroke unit was studied with C-EEG for a mean duration of 17.5 h [49]. Two patients (2%) had NCSz, both in the acute ischemic group. Therefore, the evidence for utilization and yield of C-EEG in acute ischemic stroke patients is poor, and these patients probably remain a low risk group. Accordingly, C-EEG for acute ischemic stroke should probably be limited to those with large infarcts involving cortex and with altered consciousness, or those with fluctuations or deficits out of proportion to the infarct size and location.

Infections of the Central Nervous System. Infection of the central nervous system (CNS) is an established risk factor for seizures, particularly with viral infections (nearly 50% in patients with herpes encephalitis) as opposed to bacterial infection (15%) [50, 51]. A retrospective study monitored patients with suspected CNS infections for a mean duration of 2.5 days, excluding all patients who had neurosurgical procedures [15]. Of the 42 patients, 14 (33%) had seizures, of which 64% were nonconvulsive. In this cohort, 8 of 42 patients (19%) had NCSE. This may be an overestimate because the study was performed in selected patients and may not have represented the entire population with CNS infections. In this study, 67% of the population had clinical seizures prior to EEG, but there was no association between seizures prior to EEG and electrographic seizures during C-EEG. Further studies are required to assess the seizure frequency more accurately by studying a larger, unselected group of patients.

Brain Tumors. Neoplasms of the brain are an established risk factor for seizures and epilepsy. In a recent prospective study of critically ill patients in the Neuro ICU, those with a history of brain tumors had one of the highest associations, of all causes, with NCSz or NCSE [37]. Very infrequently, NCSE can be the presenting manifestation of metastatic and primary brain tumors [52, 53]. In a cohort of 259 patients with brain tumors who underwent C-EEG monitoring, 2% had NCSE, of which half were purely nonconvulsive [54]. Treatment resulted in resolution of NCSE in 22 of 24 patients (92%), indicating not only the high incidence of NCSE in this population, but also that it is easily treated, making it important to monitor these patients with C-EEG.

Patients With Systemic Illness and Altered Mental Status Without Neurologic Injury. Seizures are common in critically ill patients who do not have a primary brain insult. Retrospective study of all patients in the medical ICU (majority with sepsis) undergoing C-EEG and without a known neurologic injury found that 10% had electrographic seizures, 67% of which were purely nonconvulsive; it was unclear how many qualified as NCSE [23]. Also, the incidence of periodic discharges was 67% in this population. In a prospective study of 100 patients with sepsis and altered mental status, the incidence of NCSz was similar (11%), with all seizures considered definite or possible NCSE; 1-year follow up showed that none of the 35% of patients who survived developed subsequent unprovoked seizures [19]. There have been conflicting results concerning outcomes and any association with mortality for these patients with NCSz, which remain areas for research [19, 23].

Metabolic derangement, sepsis, and delirium are common in the postoperative period and make patients more susceptible to seizures. Kurtz and colleagues studied 154 patients undergoing C-EEG in a surgical SICU, mostly (65%) after abdominal surgery [55]. All patients with primary neurologic problems or neurosurgical intervention were excluded. With a minimum of 12 h of monitoring, NCSz were observed in 16% of patients, including 5% with NCSE; 29% had periodic discharges. Multivariate analysis identified coma and clinical seizures prior to C-EEG as predictors of NCSz. Kamel and colleagues studied all patients admitted to the MICU and SICU (excluding those with primary brain insults) and found NCSz in 11%, but the incidence of NCSE was not reported [56].

Cardiac Arrest Requiring Therapeutic Hypothermia and Pharmacologic Paralytics. Seizures are seen in 10–30% of patients with cardiac arrest who are treated with therapeutic hypothermia (TH) [57–59]. Seizures occur during the cooling phase, not just during the rewarming phase of TH [59]. During the cooling phase, patients are often paralyzed pharmacologically to prevent shivering and to maintain temperature goals—potentially masking the motor manifestations of seizures. C-EEG is thus required to detect NCSz and facilitate appropriate treatment. Cardiac arrest survivors also have frequent myoclonic seizures and myoclonic SE, and C-EEG is also required to differentiate epileptic from non-epileptic or subcortical myoclonus, although both are treated similarly. The neurointensive care guidelines from European Society of Intensive Care Medicine (ESICM) recommend C-EEG during the TH phase and for 24 h after rewarming for detection of NCSz [39]. Some institutions, including ours, have a protocol to monitor the patients continuously for 72 h beginning as soon as possible, but always within the first 12 h after arrest.

Patients With Routine EEG Showing Malignant Periodic Patterns. Several different periodic patterns can be found on the EEGs of critically ill patients. Studies in adults and children have shown that generalized periodic discharges (GPDs) are strongly associated with NCSz and NCSE [60, 61]. Similarly, lateralized periodic discharges (LPDs) (often labeled periodic lateralized epileptiform discharges, or PLEDs earlier) and lateralized rhythmic delta activity (LRDA) have a high association with acute seizures [62–64]. In a retrospective study, the incidence of seizures in patients with LRDA was 63%, similar to that associated with LPDs (57%) [63]. Patients who have these patterns on routine EEG should be monitored for 24–48 h due to the high risk ($\geq$50%) of developing seizures (mostly nonconvulsive). More details on periodic EEG patterns in critically ill patients are described in Chap. 5, "Periodic EEG Patterns".

Patients With Abnormal Movements Or Other Subtle Signs of Possible Seizure Activity. Critically ill patients often have paroxysmal movements, such as tremors, myoclonus, clonus, paroxysmal abnormal movements of the mouth or eyes, posturing, and autonomic events that can mimic epileptic seizures. It is often difficult to determine whether these events are epileptic or not without continuous

video EEG. One retrospective study examined all EEGs performed for observed movements in the ICU and found that 73% of the episodes were non-epileptic [65]. Therefore, video EEG is important in these patients, not only to make a diagnosis of seizures, but also to exclude seizures and prevent unnecessary use of ASDs.

Assessing the Efficacy of Treatment for Seizures and Status Epilepticus

The recent American Clinical Neurophysiology Society (ACNS) guideline for C-EEG in critically ill patients recommends that patients with previous CSE and those being treated for NCSE should be monitored for at least 24 h after cessation of all electrographic seizures. It is also recommended that critically ill patients being weaned off ASDs should be monitored for at least 24 h after stopping the medication [39]. For medications with long half-lives, longer monitoring is reasonable in selected cases.

Refractory status epilepticus (RSE) is defined as ongoing clinical or electrographic seizures despite adequate initial treatment with at least a benzodiazepine and one other appropriately chosen ASD [3]. Prolonged RSE is almost always nonconvulsive (even if it began as CSE), and all patients with RSE being treated with anesthetic doses of IV ASDs should be monitored continuously to assess treatment efficacy.

Duration of Monitoring

The recent ACNS consensus statement recommends monitoring for at least 24 h for critically ill patients with suspected NCSz [2]. In a retrospective study of 570 consecutive patients with unexplained alteration of consciousness, 88% had seizures detected within first 24 h of recording [16]. In the non-comatose patients, 95% of seizures were detected in 24 h of recording, and 98% after 48 h. In the comatose patients, however, only 80% of seizures were detected after 24 h, and 87% after 48 h. In comatose patients, more prolonged monitoring appears appropriate.

In places where resources are limited, early EEG findings may help determine the likely yield of prolonged monitoring. Several retrospective studies indicate that generalized slowing alone, with lack of epileptiform discharges on the initial EEG, predicts a low risk of seizures [30, 66, 67]. In one such study, no patients without epileptiform discharges in the first 4 h of recording developed seizures during subsequent monitoring—with a median monitoring duration of 24 h (range, 18–70 h) [66]. The same study, extended to 625 patients, found that if no seizures occurred after 16 h of C-EEG, the probability of recording a subsequent seizure decreased to <5% in patients with epileptiform discharges; in those patients without epileptiform discharges, this 5% threshold was reached after only 2 h [30] (Figs. 23.3 and 23.4).

Diagnosis of Nonconvulsive Seizure

Diagnosis of NCSz is often difficult or impossible without EEG as clinical manifestations may be very subtle. Even with C-EEG, the diagnosis can be difficult in critically ill patients. An electrographic seizure is defined as continuous rhythmic or periodic epileptiform discharges at >2.5 Hz, or epileptiform discharges that evolve in frequency, morphology, or location, and last at least 10 s (see Table 23.1). In critically ill patients, however, the background, interictal activity, and seizures are quite different as compared to those in otherwise healthy individuals. Thus, it can be difficult to distinguish ictal patterns (i.e., electrographic seizures) from interictal ones. Based on expert opinion, criteria have been proposed to define NCSz (see Table 23.1) [5]. Rhythmic discharges or periodic patterns >2.5 Hz are generally considered ictal, and those <1 Hz nonictal. Still, periodic patterns between 1 and 2.5 Hz (inclusive) may represent ictal or interictal phenomena based on different modifiers and are often considered to lie on an ictal-interictal continuum (IIC) (Figs. 24.3 and 24.4) [68, 69], but it is often challenging to make a diagnosis of NCSz based on EEG alone. In clinical practice, a trial of a rapid acting IV ASDs, e.g., benzodiazepines (BZDs) or less sedating IV ASDs such as phenytoin, valproate, lacosamide, or levetiracetam may be used to try to distinguish ictal from interictal activity. Because BZDs can abolish many kinds of abnormal electrical activity, the electrographic improvement must be accompanied by clinical improvement to make a definite diagnosis of NCSE. In one study, Hopp and colleagues found that in a cohort of 62 patients with suspected NCSE, a trial of IV BZD lead to *clinical* improvement in 35% [70]. All responders survived and had good functional outcomes. In clinical practice, however, the sedating effects of BZDs can confound the trial results, especially if large doses are used. Another recent study by O'Rourke and colleagues utilized BZDs or non-sedating ASDs in conjunction with clinical examination in order to identify ictal patterns [71]. They evaluated the response to BZDs and non-sedating ASDs in patients with sharp waves of triphasic morphology. Of 64 patients studied, 34.4% had a positive response (EEG and clinical improvement, though not necessarily immediately). Patients receiving non-sedating ASDs had a higher rate of definite or probable response compared to those receiving BZDs (26.7% vs. 18.9%), but the response was delayed in 20% of those given non-sedating ASDs. Our institution proposes a protocol using small, escalating doses

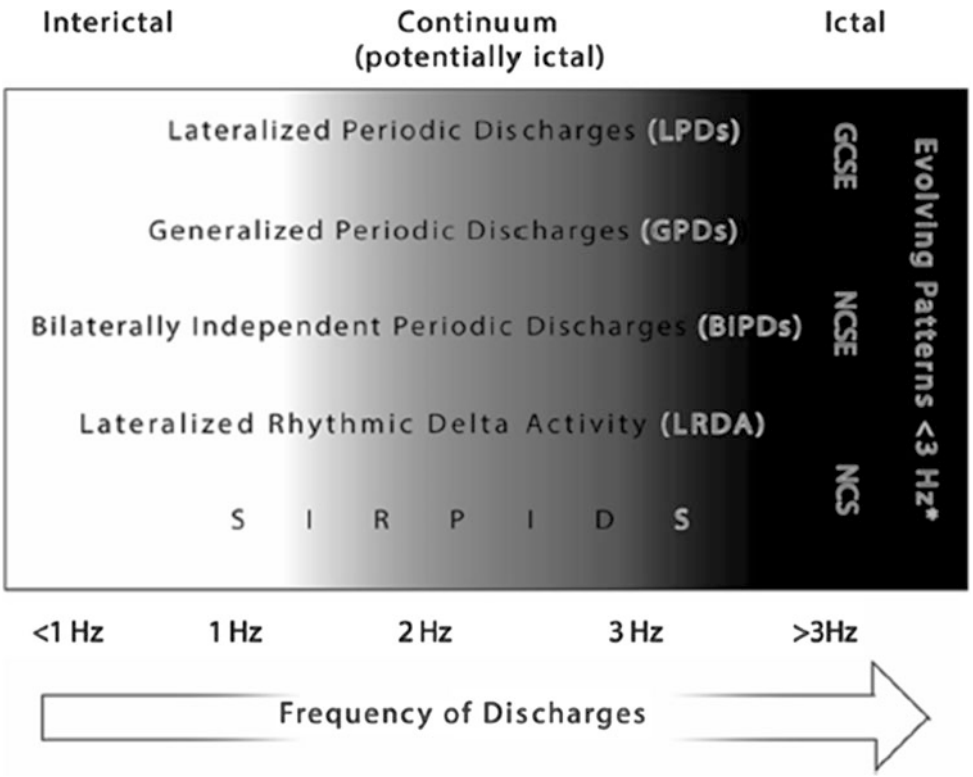


Fig. 23.3 Ictal-interictal continuum. Demonstrates various EEG patterns, primarily based on frequency, depicted along the ictal-interictal continuum. The frequency of discharges (*shown on the x-axis*) has traditionally been the benchmark guiding the aggressiveness of treatment. This frequency-based division between interictal, continuum and ictal is arbitrary, conceptual, and does not take evolution of patterns into account. The evolution of EEG patterns can be subtle, especially when observing long epochs in critically ill patients, and it is often difficult to reach a consensus. Still, the presence of even subtly evolving patterns increases the possibility of them being ictal. If a clinical correlate is present with any of these patterns, it must be considered ictal by definition, regardless of the frequency. *At least 1 Hz with clear (unequivocal) evolution in frequency, morphology, or location is considered to be ictal. *GCSE* generalized convulsive status epilepticus, *NCSE* nonconvulsive status epilepticus, *NCS* nonconvulsive seizure, *SIRPIDs* stimulus-induced rhythmic periodic or ictal discharges. Adapted from Sivaraju and Gilmore [69], with permission

of rapidly acting BZDs (e.g., midazolam) or non-sedating ASDs, and evaluating for change on the EEG and on clinical exam, i.e., resolution of the EEG abnormality and unequivocal improvement in clinical exam, or improvement of the EEG with return of previously absent normal EEG patterns, such as sleep spindles or a posterior-dominant rhythm (Table 23.2) [72].

Data Analysis and Review

Continuous EEG monitoring of critically ill patients generates plentiful data, and its review can be time-consuming and tedious. Therefore, while EEG provides time-sensitive data, it may be difficult to review in a timely manner given the time and expertise required. Review of the raw EEG in several patients being monitored simultaneously adds to the clinical neurophysiologist's burden. Recent ACNS guidelines recommend that data be reviewed by a trained neurophysiologist at least twice daily, and reported formally at least daily. For patients with SE, the EEG should be reviewed as frequently as required to provide timely input to the clinical team. The raw EEG, preferably with additional quantitative EEG (Q-EEG), should be left open and available at the bedside and remotely for real-time review at all times. In recent years, Q-EEG techniques have improved enough to assist greatly in the rapid review of prolonged EEG monitoring.

Quantitative EEG

Quantitative EEG (Q-EEG) techniques allow compression of the raw EEG data into a graphic representation of hours of an EEG at a time, enabling highlighting of significant electrographic events and trends over long periods, thereby expediting the review process. Many different algorithms and software programs are being utilized, but in essentially all Q-EEG techniques, the data from raw EEG is extracted, compressed, and displayed graphically. Some commonly

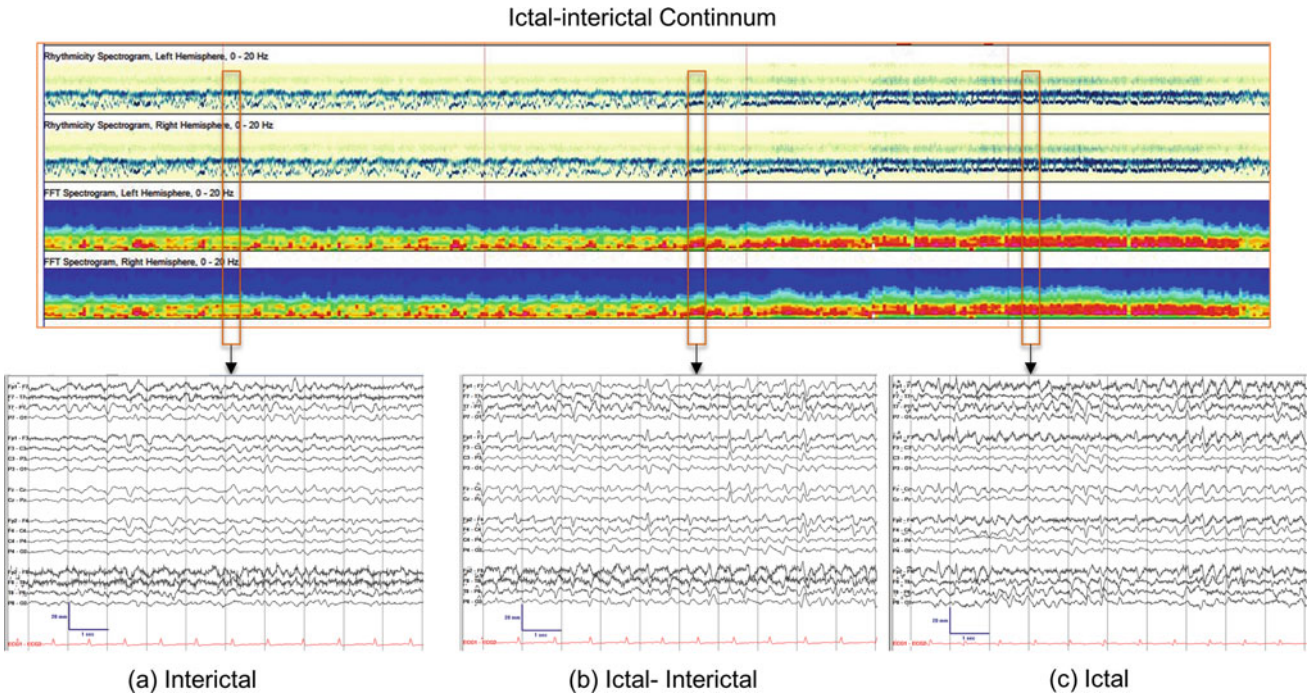


Fig. 23.4 Quantitative EEG and raw EEG on the ictal-interictal continuum. Patient is a 75-year-old woman with a history of cerebellar stroke and multiple vascular risk factors who presented with a change in mental status and was found to have sepsis. She continued to show the same impaired consciousness despite appropriate treatment of her infection and was metabolically and hemodynamically stable. The figure shows a gradual transition over an hour from interictal to ictal without a clear cut off, demonstrating the ictal-interictal continuum. The *top* portion of the figure shows 1 h of quantitative EEG, with time on the x-axis and frequency (0–20 Hz) on the y-axis (from Persyst 12™, Persyst Inc., San Diego, California). The *top 2 rows* are the rhythmicity spectrogram, showing gradually increasing rhythmicity, shown by the darkening tracing as time progresses to the right. The *bottom 2 rows* show the color density spectral array (CDSA), showing gradual evolution in the pattern over this hour (increasing delta and theta slowing as time progresses). The *bottom panel* shows the associated raw EEG for 10 s from 3 different time points. (EEG settings: sensitivity: 7 uV; low-frequency filter: 1 Hz; high frequency filter: 70 Hz; and notch filter turned off). **a** The initial epoch shows a background of quasi-rhythmic theta and delta slowing with only a hint of periodic discharges, interpreted as interictal. **b** There is gradual increase in frequency and prominence of generalized periodic discharges, on and off from 1.5 to 2.5 per second; this is considered to lie on ictal-interictal continuum. **c** The EEG shows the frequency of the GPDs at 2.5 Hz, evolving to 3–3.5 Hz rhythmic activity in the second half of this figure, and thus considered ictal, i.e., an ongoing seizure

used Q-EEG techniques and their utility in management of NCSz are described below (Fig. 23.5).

Color density spectral array (CDSA) utilizes fast-Fourier transformation (FFT) applied to raw EEG, which demonstrates the changes in power (defined as sum of the area under the curve, i.e., the square of voltages, measured in microvolts, (uV^2) for a defined period of time), recorded at different frequencies in different colors on the y-axis. Amplitude integrated EEG (aEEG) produces a time-compressed display of raw EEG signal using a semi-logarithmic scale of amplitude, showing both the lowest and highest amplitudes in each short epoch. Rhythmicity spectrograms show how rhythmic (or periodic) the EEG is at each frequency. Seizures typically produce a diagonal pattern, showing rhythmic activity changing gradually in frequency, a pattern almost pathognomonic for seizures. Asymmetry-based Q-EEG trends are also helpful in seizure detection. Relative asymmetry spectrogram compares the power between homologous electrodes, thereby measuring the asymmetry between right and left hemispheres; focal seizures arising from one hemisphere can be detected as an increase in power on that side. All of these Q-EEG techniques can be run on one channel, a group of channels, or for a whole hemisphere.

Several studies have investigated the diagnostic utility and accuracy of Q-EEG tools in seizure detection in critically ill adults and children. In neonates, aEEG has been used for many years to study the EEG background and more recently for seizure detection, as well (though we caution strongly against relying on aEEG alone, because there can be many false positives). In a retrospective study of critically ill children, the sensitivity of CDSA was 83.3%, and that of aEEG 81.5% for seizure detection when reviewed by a neurophysiologist who was trained briefly and blinded to the raw EEG [73]. About 10.5% of seizures were missed on both tests, typically seizures that were focal, low amplitude (<70 uV), shorter in duration (<1 min), or occurring in the context of abundant epileptiform discharges. aEEG in adults

Table 23.2 Anti-seizure drug trial for the diagnosis of nonconvulsive status epilepticus (From Hirsch and Gaspard [72], with permission)

• Indication
Rhythmic or periodic focal or generalized epileptiform discharges on EEG with neurologic impairment
• Contraindication
Patients who are heavily sedated or paralyzed
• Monitoring
EEG, pulse oximetry, blood pressure, electrocardiography, respiratory rate with dedicated nurse
• Anti-seizure drug trial
Sequential small doses of rapidly acting short-duration benzodiazepine such as midazolam at 1 mg/dose or non-sedating IV anti-seizure drug such as levetiracetam, valproate, fosphenytoin, or lacosamide
Between doses, repeated clinical and EEG assessment
Trial is stopped after any of the following:
1. Persistent resolution of the EEG pattern (and exam repeated)
2. Definite clinical improvement
3. Respiratory depression, hypotension, or other adverse effect
4. A maximum dose is reached (such as 0.2 mg/kg midazolam, though higher doses may be needed if the patient is on chronic benzodiazepines)
• Interpretation
The test is considered positive ("definite NCSE") if there is resolution of the potentially ictal EEG pattern AND either an improvement in the clinical state or the appearance of previously absent normal EEG patterns (e.g. posterior-dominant "alpha" rhythm)
If EEG improves, but patient does not, the result is equivocal ("possible NCSE")
Nonictal patterns may disappear after administration of benzodiazepines (always without clinical improvement)
Administration of too high a dose of benzodiazepine might improve the EEG but also leads to sedation, preventing the detection of clinical improvement
Negative or equivocal response does not exclude NCSE

has been studied less well for seizure detection but can be useful in conjunction with other trend analysis and the full, raw EEG. aEEG is also useful for detection and monitoring of suppression-burst patterns, often used as an EEG target when sedatives are used for treatment of RSE or elevated intracranial pressure. In addition to aEEG, the suppression index (percent of the EEG record below a set voltage threshold, usually 5 or 10 uV) is also useful for managing iatrogenic coma.

Williamson and colleagues assessed the utility of CSDA in critically adults. With blinding to the raw EEG, they found a detection rate of 89% of 1190 seizures when reviewed by Q-EEG-naïve and briefly trained Neurology residents [74]. Despite the reasonable detection rate, there were many false positives. Another study compared the rate of seizure detection by neurophysiologists, EEG technologists, and ICU nurses when examining different Q-EEG panels such as the rhythmicity spectrogram, CDSA, asymmetry index, and aEEG (without accessing the raw EEG) and found similar sensitivities (0.87, 0.80, and 0.87) and specificities (0.61, 0.80, 0.61, respectively) [75]. Similarly, Dericiolglu and colleagues showed that non-neurophysiologists and ICU nurses were able to identity seizures using aEEG and CDSA with accuracy similar to an epileptologist's, with good inter-rated agreement ($\kappa = 0.79$–0.81) [76]. Once again, seizures of lower voltage and shorter duration were often missed. CDSA was also effective in detecting cyclic seizures, which are fairly common in critically ill patients and may not be identified on raw EEG [77]. Most of these studies did not allow reviewers to visualize the raw EEG, likely contributing to the high false positive rates. Moura and colleagues compared the sensitivity of seizure detection and the time required to review 24-h studies between a conventional review method and review of the study using CDSA guidance, allowing review of the underlying raw EEG at the time of CDSA changes [78]. The average review time when using CDSA guidance was significantly shorter than that of conventional review of the full raw EEG data alone (8 ± 4, vs. 38 ± 17 min), even when records contained seizures (10 ± 4, vs. 44 ± 20 min). Sensitivity of seizure detection using CDSA-guided review remained high, at 87.3%.

In summary, these studies suggest that Q-EEG is very promising for easier and faster detection of seizures in ICU patients. It can also be taught to ICU nurses, EEG technologists, residents, and others who can potentially utilize it at the bedside and recognize possible seizures in a timely manner—to be confirmed by neurophysiologists later using

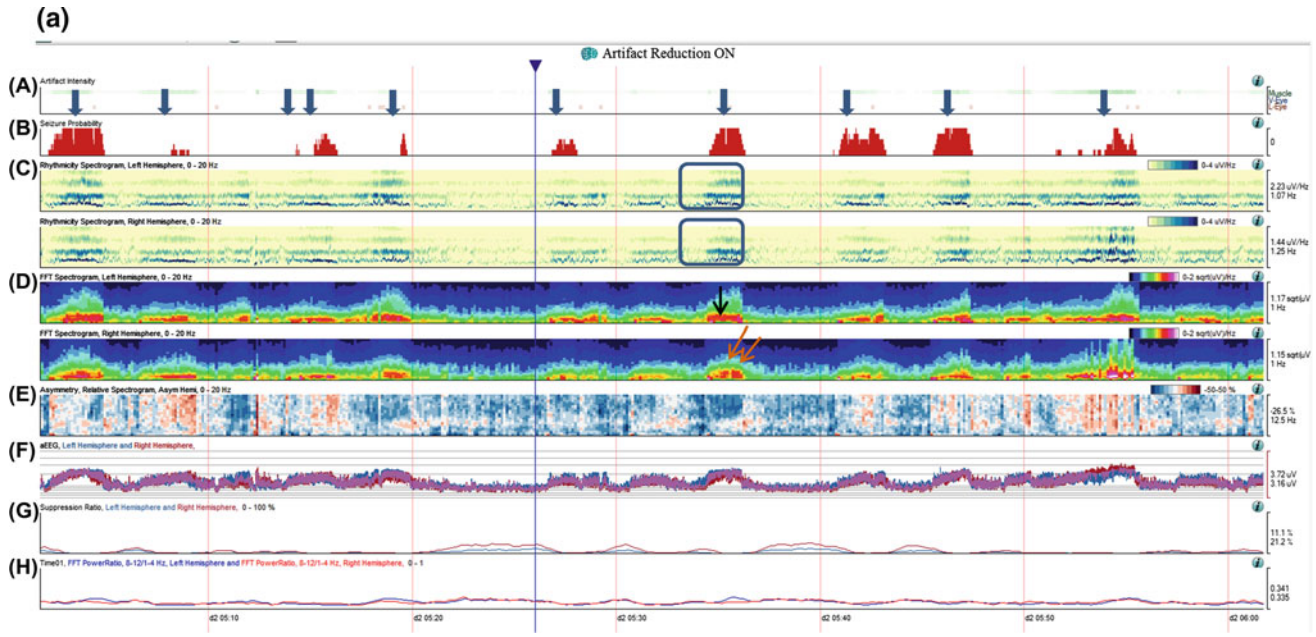


Fig. 23.5 **a** Quantitative electroencephalography (Q-EEG): (comprehensive panel view) from Persyst 12™ (Persyst Inc., San Diego, California) of a 92-year-old right-handed woman with an acute left hemisphere subdural hematoma who underwent evacuation with a left craniotomy and was found to have multiple (10–11) nonconvulsive seizures per hour arising from the left hemisphere This is a 4-h epoch of Q-EEG page showing long-term trends: *A* Artifact intensity: displays the amount of muscle and other artifact. The artifact reduction feature of Persyst can be used when there is excess artifact for any reason. *B* Seizure probability as determined by Persyst seizure detection algorithm. Most of the seizures in this patient were detected by this algorithm, as indicated by *red bars*. *C* Rhythmicity spectrogram for left and right hemispheres: displays rhythmic components of different frequencies, *darker colors* being more rhythmic. Seizures are detected as a sudden increase in rhythmicity of delta and theta frequencies (*square box*). *D* FFT spectrogram for left and right hemispheres: power of different frequencies is displayed as different *colors* on the *z*-axis (*color is the* '*z-axis*'; *see color scale*). During seizures, there is a flame-shaped increase in delta power, as displayed by the increase in *red* (*slower frequencies—single black arrow*) and *green colors* (*higher frequencies—double arrows*). *E* Relative asymmetry spectrogram: compares the power of different frequencies at homologous electrodes in each hemisphere (*blue* if higher power on the left, and *red* if on the *right*). *F* Amplitude integrated EEG: displays filtered and smoothed EEG amplitude (*y-axis, with a semi-log scale*) across time (*x*-axis) (*blue for left*, *red for right*, *and pink for overlapping left and right*). *G* Suppression percentage: percent of the EEG record that is below a determined threshold amplitude. *H* Alpha/delta power ratio: demonstrates alpha power over delta power, a good measure of ischemia (it decreases with ischemia) in both left (*blue*) and right (*red*) hemispheres. **b** A later 4 h epoch of Q-EEG from the same patient. The earlier part of the record shows approximately 9–10 focal seizures per hour, maximal on the left. **c** After treatment with IV ASD, the seizures ceased (by halfway through this epoch). **d** Raw EEG of a nonconvulsive seizure (EEG settings: 7 uV; low-frequency filter: 1 Hz; high frequency filter: 70 Hz; and notch filter turned off) Seizures began with 1 Hz delta slowing with periodic spikes in the left fronto-central region (*top row*), which then increased gradually to 1.5 Hz, evolve in morphology, and spread to the entire left and right hemisphere (*middle row*), beginning 47 s after onset, followed by abrupt offset after 2 min and 21 s of onset (*bottom row*). **e** Raw interictal EEG

review of the raw EEG. Nevertheless, most such studies had high false positive rates, and review of the raw EEG is still required to confirm the Q-EEG findings. No single method has been demonstrated to be superior to another in the detection of seizures, but a combination of methods may work well. Finally, once a seizure pattern has been recognized and established for a given patient, automatic seizure detection parameters may be set to identify subsequent seizures at the bedside. Future studies are required to demonstrate if Q-EEG alone can be utilized as a tool for data review in the ICU. As artifact detection and removal, seizure detection, and other Q-EEG methods improve, computer analysis will almost certainly play a greater role in this setting.

Cost Benefit

Continuous EEG monitoring is a labor-intensive process, requiring substantial resources in finances and manpower. There is extensive evidence that NCSz and NCSE are detrimental to the brain, especially in the setting of acute brain insults. It has been shown that NCSz and NCSE are associated with worse neurologic outcomes in patients and with increased morbidity and mortality. C-EEG monitoring is the only means to detect and appropriately guide treatment for NCSz. Whether detection and timely treatment of NCSz and NCSE actually improves patient outcomes have yet to be determined. One retrospective study found that C-EEG monitoring led to changes in ASD management in 52% of

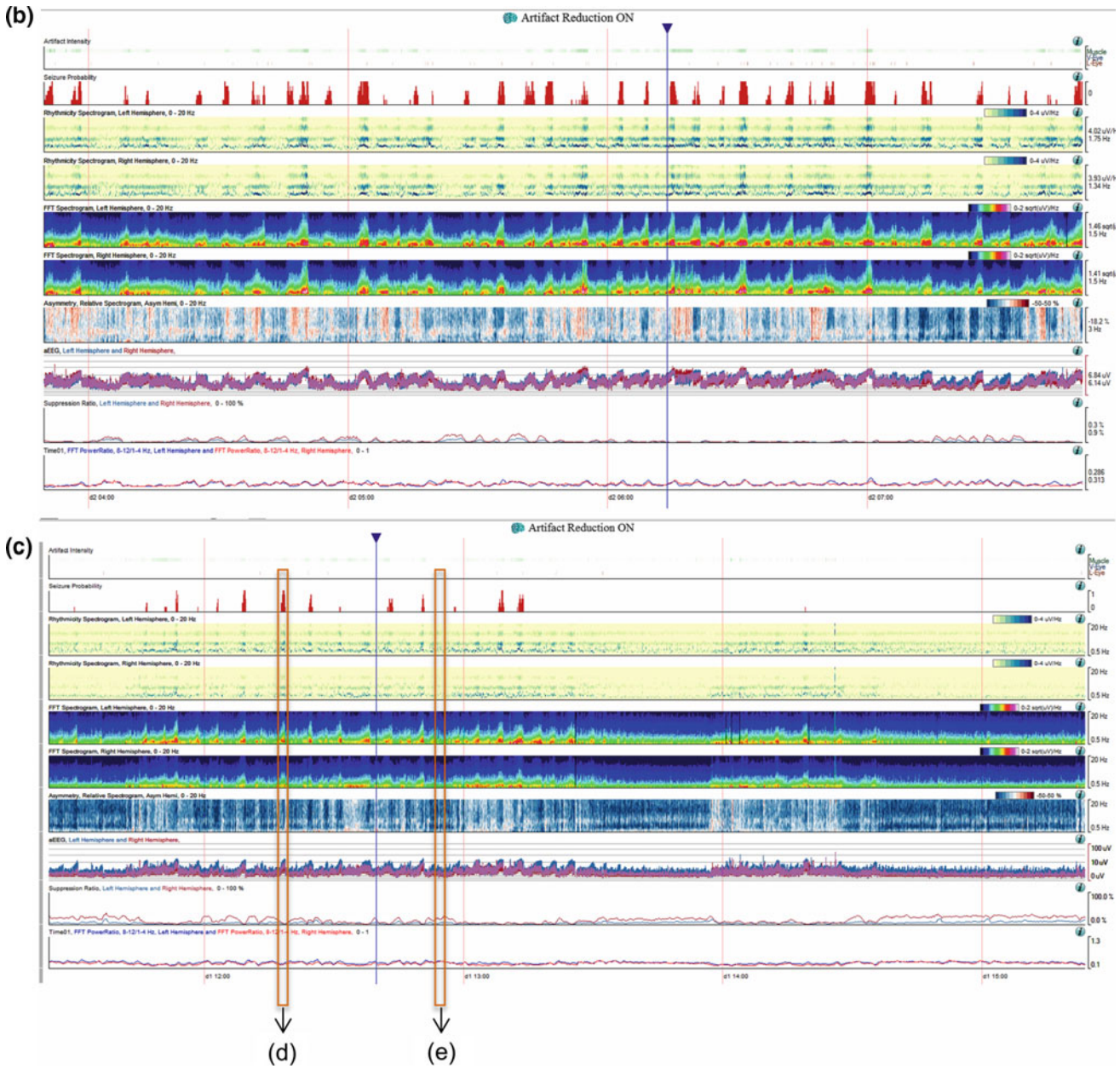
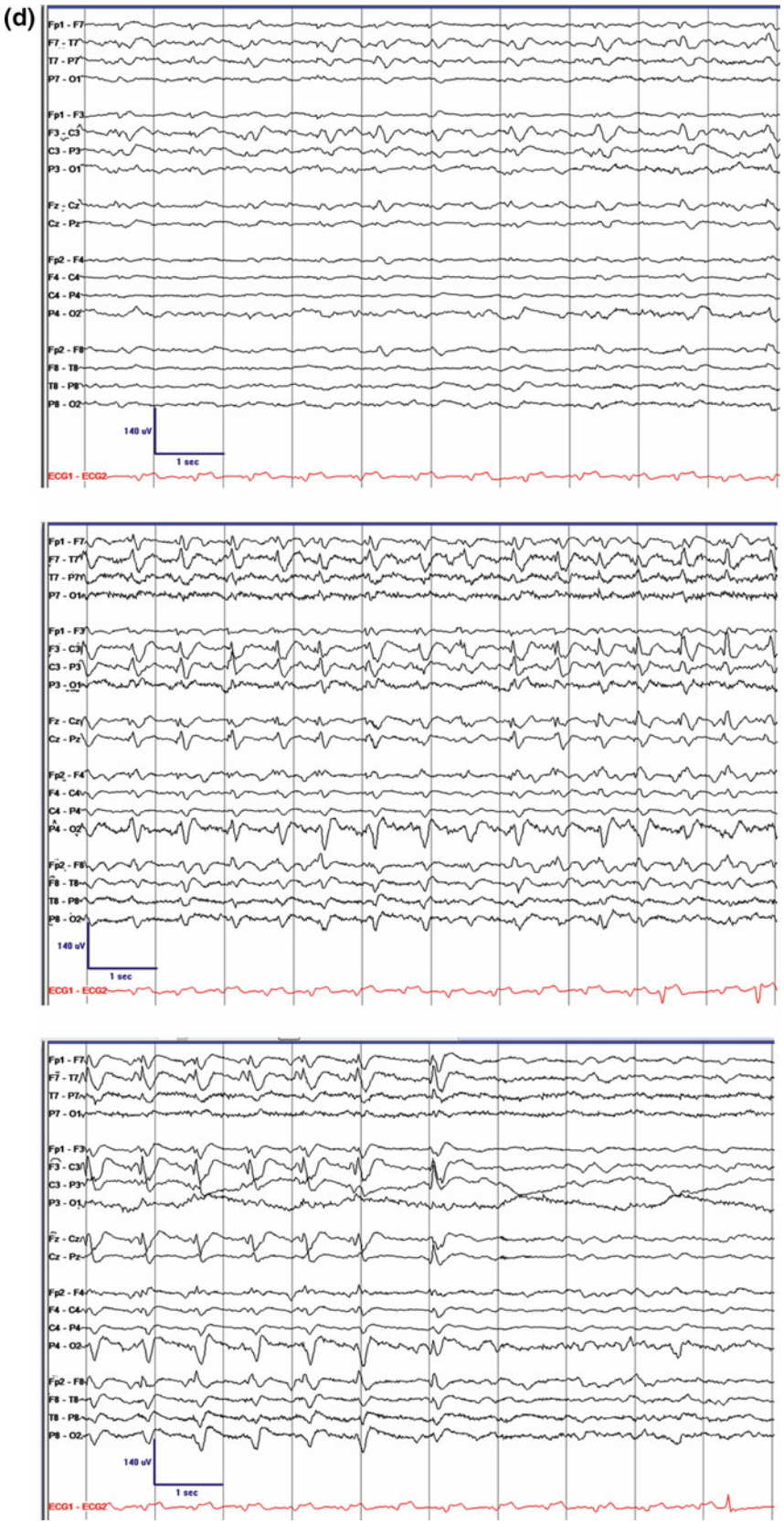


Fig. 23.5 (continued)

adult patients in the initiation, change in, or discontinuation of drugs [31]. A prospective study in critically ill children found that C-EEG led to change in clinical decision-making in 59% of patients [79]. Whether these changes in ASD management eventually led to improvement in patient outcomes is unknown.

Ney and colleagues conducted a retrospective study of mechanically ventilated patients from a nationwide inpatient administrative database and compared patient outcomes and cost of hospitalization between those using C-EEG versus routine EEGs [80]. They found that use of C-EEG was associated with significantly lower inpatient mortality, without any added cost, compared to the use of routine EEG. The big challenge still ahead is to demonstrate that the benefits of C-EEG monitoring in critically ill patients (for detection and treatment of NCSz) affect their long-term functional outcome and outweigh the cost and resources utilized. Future prospective well-designed multicenter studies are needed to answer these questions, and some such studies will have to be done in settings that do not routinely monitor all patients.



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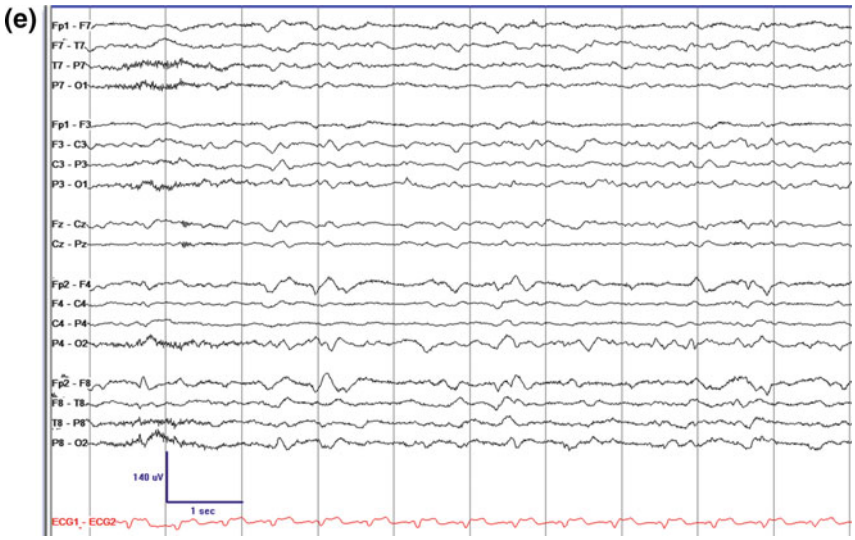

Fig. 23.5 (continued)

Conclusions

Critically ill patients are at high risk for seizures, most of which are not associated with detectable clinical signs at the bedside. This includes patients with primary brain insult such as those with TBI, ICH, SAH, ischemic stroke, and CNS infections, as well as those with systemic medical problems. C-EEG monitoring is thus required for the diagnosis and management of SE in these patients. In non-comatose patients, 24 h of recording is required to detect most patients who will develop NCSz; in comatose patients, 48 h is recommended. Patients being treated for NCSE should be monitored for at least 24 h after resolution of NCSE. The EEG findings of critically ill patients are different from those in ambulatory patients, so the diagnosis of NCSE can be difficult. Some patients have equivocal periodic or rhythmic patterns (discussed in Chap. 5) that are difficult to differentiate clearly as ictal or interictal and are considered to lie on an ictal–interictal continuum. In such situations, trials with BZDs or non-sedating ASDs, including assessment of the clinical response, can be used to diagnose possible, probable, or definite NCSE. Finally, as review of C-EEG data can be laborious and time-consuming, various Q-EEG methods can be used to expedite the process with only modest loss of sensitivity for seizures or epileptiform patterns. We recommend using Q-EEG only in conjunction with a review of the raw EEG to avoid false positives and hence inappropriate treatment.

C-EEG monitoring has emerged recently as a critical tool for the diagnosis and management of NCSE. Its markedly increased use has led to the recognition of previously undiagnosed nonconvulsive seizures. Many recent studies using implanted electrodes have shown that nonconvulsive seizure and periodic patterns are associated with increased metabolic demands, and may cause secondary neuronal injury [81]. Still, many questions still remain. Whether seizures are the manifestations of underlying insults, or contribute to additional neuronal injury, or both, is very difficult to determine in an individual patient. Teasing apart the ictal and interictal component of the ictal–interictal continuum, and more importantly when these patterns are causing neuronal injury (whether "ictal" or "interictal"), will be critical for guiding appropriate management for these patients. Finally, whether diagnosis and aggressive treatment of NCSz translates into better patient outcomes have yet to be demonstrated. Future, large prospective multicenter studies are required to answer these questions.

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The Management of Nonconvulsive Status Epilepticus in Adults

24

Suzette M. LaRoche and Hiba A. Haider

Introduction

The increasingly widespread use of continuous electroencephalography (C-EEG) in critically ill patients has led to the recognition that nonconvulsive status epilepticus (NCSE) is a more common condition than previously recognized. Clinical and EEG classifications for NCSE have changed over time and currently there is no universally accepted definition [1–5]. The original definition followed that of previous versions of generalized convulsive status epilepticus (GCSE): a condition of ongoing seizure activity lasting >30 min, or intermittent seizures over a >30 min period without recovery, but in the absence of accompanying convulsive activity [1, 6]. In patients with baseline coma or encephalopathy, a definition of NCSE has been proposed as either 30 total minutes of ictal EEG activity in any given hour (i.e., consistent with an electrographic seizure), or seizure activity for >50% of a prolonged EEG recording [7]. The Neurocritical Care Society has suggested shortening the 30 min requirement to 5 min, as a single seizure that lasts longer than 5 min is likely to persist or recur, and might functionally represent status epilepticus (SE) [6]. Additionally, according to a consensus of the International League Against Epilepsy (ILAE), SE was recently described in terms of the time at which mechanisms that terminate seizures fail (time point 't1') and the time at which long-term sequelae, including neuronal death and alteration of neuronal networks, generally ensues (time point 't2') [1]. For GCSE, animal models indicate that these time points are 5 and 30 min, respectively. For NCSE, however, time points are not well established.

S.M. LaRoche (✉)
Department of Neurology, Mission Health System, Emory University School of Medicine, 509 Biltmore Ave, Asheville, NC 28801, USA
e-mail: suzanne.laroche@gmail.com

H.A. Haider
Division of Epilepsy, Emory University School of Medicine, 12 Executive Park Dr NE, Atlanta, GA 30329, USA
e-mail: hiba.arif@emory.edu

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Several other classifications of NCSE have been described based on clinical features, EEG correlates, etiology, and pathophysiology [2, 8–10]. The lack of consensus on what constitutes NCSE reflects the fact that EEG findings do not exist in isolation, but occur in the setting of a variety of pathologic conditions that differ based on age, cerebral development, and epilepsy syndrome(s).

Incidence

Nonconvulsive status epilepticus is common in comatose patients, with an estimated prevalence between 5 and 48% [11]. Studies have demonstrated that NCSE accounts for at least one-third of all cases of status epilepticus (SE) [12]. Although more commonly seen after clinical seizures, NCSE can also present in comatose patients with no overt signs of seizure activity. Population-based studies of the incidence of NCSE are limited, but small studies demonstrate different burdens of NCSE across various cohorts. NCSE accounts for up to 20% of all cases of inhospital SE [13], and up to 47% in the intensive care unit (ICU) [14, 15]. NCSE is often the cause of altered mental status in critically ill patients without a known acute neurologic condition, such as those in the medical ICU with underlying sepsis [16–19].

The Role of Etiology

NCSE was first described in ambulatory patients with chronic epilepsy, but has since been increasingly recognized in the setting of critical illness. As the vast majority of patients identified as having NCSE are now diagnosed in this context, this chapter will focus on NCSE in critically ill patients. Improvement in the detection of nonconvulsive seizures (NCSzs) and NCSE is attributable not only to the recent increased use of C-EEG but also to increased awareness of the prevalence of NCSE. Up to 50% of patients

Table 24.1 Common conditions associated with and nonconvulsive status epilepticus; adapted from Herman and colleagues [37] with permission . [Percentage of patients in each condition found to have nonconvulsive seizures or nonconvulsive status epilepticus.]

	Adults	Children	References
Following convulsive status epilepticus	48%	26–57%	[21, 25, 29–34]
Epilepsy-related	33–39%	11–71%	[20–28]
Sepsis-associated encephalopathy	32%	58%	[16–19]
Recent neurosurgical procedures	23%	71%	[22, 28, 38]
Brain tumors	Any seizure: 23–37% NCSE: 9–12%	19–66%	[16, 21, 24, 28, 39–41]
Moderate-to-severe traumatic brain injury	18–33%	14–70%	[16, 21, 22, 24, 32, 38, 42–47]
Intraparenchymal hemorrhage	16–23%	11–100%	[22, 24, 26–28, 34, 38–40, 48–50]
Hypoxic-ischemic injury following cardiac or respiratory arrest, with or without therapeutic hypothermia	10–59%	16–79%	[16, 21, 22, 24, 28, 32, 34, 38, 47, 51–59]
Central nervous system infections	10–33%	16–100%	[16, 21, 22, 24, 26, 28, 32, 34, 38, 42, 60, 61]
Aneurysmal subarachnoid hemorrhage	Any seizure: 10–19% NCSE: 3–13%		[22, 28, 62–66]
Acute ischemic stroke	6–27%	20–71%	[21, 22, 24, 26–28, 38–40, 48, 50, 67]
Extracorporeal membrane oxygenation	N/A	21%	[59]
Drug-induced – BZD withdrawal – Psychotropic drugs (TCA, lithium, neuroleptics) – Antibiotics (beta lactams, esp. cefepime; fluoroquinolones)	<5%		[68, 69]

BZD benzodiazepine; *TCA* tricyclic antidepressants

with any type of SE have a prior diagnosis of epilepsy [20–28], with common precipitants including noncompliance with ASDs, alcohol, intercurrent illness or infection, sleep deprivation, or the progression of the underlying disease. About 5% of all adults with epilepsy will have at least one episode of clinical or convulsive SE in the course of their epilepsy [29–31], and in children the proportion is even higher (10–38%) [21, 25, 32–34]. Although NCSE can be a manifestation of an epileptic syndrome itself, most initial episodes of NCSE in epilepsy seem to be triggered by changes in ASDs [35] or interactions with concurrent medications that lower serum levels of ASDs [36].

In critically ill patients, the most common causes of NCSE are similar to those of convulsive SE (Table 24.1 [37]) [16–34, 38–69]. Most cases of NCSE in the critically ill are the result of an acute cerebral insult such as subarachnoid hemorrhage [22, 28, 62–66], infections or inflammatory conditions of the central nervous system [16, 21, 22, 24, 26, 28, 32, 34, 38, 42, 60, 61], brain tumors [16, 21, 24, 28, 39–41], ischemic [21, 22, 24, 26–28, 38–40, 48, 50, 67] and hemorrhagic [22, 24, 26–28, 34, 38, 40, 41, 49–51] strokes, traumatic brain injury [16, 21, 22, 24, 32, 38, 42–47], or anoxia [16, 21, 22, 24, 28, 32, 34, 38, 47, 51–59]. As NCSE in the critically ill encompasses a heterogenous group of etiologies, it is associated with a corresponding variety of prognoses. These etiologies and their prognoses are discussed here because it is important to weigh the risks and benefit of aggressive treatment against the expected outcome.

Cerebrovascular Insults

There are limited studies investigating the association between ischemic stroke and NCSE, but they indicate that of the 9% of patients with acute stroke who develop SE, NCSzs and NCSE are more common than are convulsive seizures [27, 28]. Effects of injuries from status epilepticus and cerebral ischemia might act in synergy to increase mortality, but this effect has not been noted to be specific to NCSE.

Only 10% of all strokes are due to intracranial hemorrhage (ICH), but ICH carries a higher mortality than ischemic stroke (almost 40%). Seizures occur in up to 28% of patients with ICH undergoing C-EEG monitoring, and up

to 18% have NCSE, although NCSE was not an independent predictor of worse outcome in these patients [49].

More data are available about the association of NCSE with subarachnoid hemorrhage (SAH). NCSE occurs in 8% of patients with aneurysmal SAH [62], a proportion that increases with the severity of the cerebral insult [63], while the incidence of NCSE in spontaneous non-aneurysmal SAH is lower, at 3% [64]. A systematic review of 18 studies that included C-EEG monitoring of 481 patients with aneurysmal SAH found that NCSzs were diagnosed in 7–18% of patients, and NCSE was diagnosed in 3–13%. Among the entire population of patients with SAH, NCSE was associated with older age (NCSE 68 years, vs. population mean 53.9 years) and higher mortality (NCSE 82–100%, vs. population mortality 13%) [70]. In a prospective study, persistence of NCSE beyond the 5th day following SAH was associated with a mortality of 100% [62].

Traumatic Brain Injury

NCSzs occur in up to 10% of patients with traumatic brain injury (TBI) [43], with 30% presenting in the first three days after injury [44]. Seizures after TBI can lead to additional neuronal injury, but it is not clear how much injury is caused by the seizures themselves versus the result of elevated intracranial pressure or perturbation of cerebral metabolism directly related to TBI. Nevertheless, seizures after TBI can result in hippocampal atrophy on MRI ipsilateral to the seizure onset [71].

Encephalitis

Noninfectious encephalitides such as autoimmune encephalitis lead to seizures in up to 78% of patients, most of which are nonconvulsive [72]. Another study of patients with encephalitis found a total incidence of SE of 18%, but the proportion of these patients with nonconvulsive versus convulsive seizures was not reported [73]. Furthermore, autoimmune encephalitis is the most commonly identified cause of new-onset refractory status epilepticus (NORSE). Mortality associated with encephalitis ranges from 5 to 30% and is not significantly different among various etiologies (whether infectious or noninfectious).

Hypoxic-Ischemic Brain Injury

SE occurs in up to 30% of patients who remain comatose after surviving cardiorespiratory arrest and is often nonconvulsive [74]. SE is not regarded as the principal cause of coma or the main driver of outcome, and the poor prognosis in patients with post anoxic coma is likely due to the anoxic injury itself [75]. NCSE after anoxic brain injury is thus considered a different entity from NCSE due to other etiologies, as the underlying brain damage is largely irreversible and usually associated with an extremely poor outcome. Markers of favorable outcome in these patients include age <65 years, return of spontaneous circulation during resuscitation, reactive pupillary and motor reflexes 3 days after arrest, and continuous, reactive EEG background [76–79]. In such cases, a treatment trial of ASDs is warranted and might improve outcome.

Medication-Induced

Less commonly, NCSE can be drug-induced. This is an important etiology to recognize because effective treatment usually requires discontinuation or dose adjustment of the offending agent [68, 69, 80]. NCSE due to beta-lactam antibiotics, particularly cephalosporins such as cefepime, has been well described [81, 82]. Other drugs associated with NCSE include fluoroquinolones [83], ifosfamide [84], L-asparaginase [85], and cisplatin [86]. In some cases, NCSE is a presentation of posterior reversible leukoencephalopathy syndrome (PRES) [87]; commonly implicated drugs include tacrolimus, cyclosporine, and bevacizumab. NCSE has been reported after sudden antagonism or withdrawal of analgesics, ASDs, sedatives, and anesthetics, especially after chronic treatment. Although recreational stimulant drugs such as amphetamine and cocaine have been associated with convulsive seizures, NCSE is not common, but there have been reports of NCSE following MDMA ('ecstasy') use [88].

Clearly, not all causes of SE carry a similar prognosis. A patient with chronic epilepsy with NCSE due to ASD noncompliance typically has a very good prognosis. On the other hand, NCSE in a comatose patient with an acute brain injury has a much worse prognosis, particularly in older patients. In addition to the prognosis of SE as linked to etiology, the prognosis of the underlying etiology itself, such as stroke, may be worse if associated with an episode of SE [29]. Aside from a single study linking NCSE to worse outcome in patients with subarachnoid hemorrhage [63], there is insufficient evidence to link NCSE directly to worsening of outcome in specific etiologies.

Diagnosis

Indications for EEG

EEG forms the cornerstone for the diagnosis of NCSE and for monitoring treatment response. The vast majority of

Table 24.2 Clinical manifestations of nonconvulsive status epilepticus

Behavioral/Cognitive	Motor	Autonomic/Vegetative
Agitation	Automatisms	Abdominal sensation
Amnesia	Dystonic posturing	Apnea/hyperventilation
Aphasia/mutism	Eye deviation	Brady- and tachyarrhythmia
Catatonia	Eye blinking	Flushing
Coma	Facial twitching	Miosis, mydriasis, hippus
Confusion/delirium	Finger twitching	Nausea, vomiting
Delusions/hallucinations	Myoclonus	
Echolalia	Nystagmus	
Laughter		
Lethargy		
Perseveration		
Personality change		
Psychosis		
Singing		

seizures recorded in critically ill patients are unrecognized at the bedside and can only be diagnosed with EEG [22]. As a general rule, any fluctuating or unexplained alteration in behavior or mental status warrants an EEG to evaluate for the presence of NCSE. EEG should be a routine component in the management of the following clinical situations:

- After GCSE—Patients who present with GCSE (or even a single generalized convulsion) usually return gradually to baseline after the motor features of the seizures resolve. If the level of consciousness is not improving within 10 min of cessation of movements, or the mental status remains abnormal 30–60 min after the convulsions cease, NCSE must be considered, and an urgent EEG is advised [31]. In one prospective study, NCSE was present in 14% of 164 patients monitored after treatment for convulsive SE, and 48% had recurrent NCSzs [31].
- Critically ill patients who are obtunded or comatose—The diagnosis of NCSE in critically ill patients with obtundation or coma can be challenging because clinical manifestations are often absent or may consist only of subtle limb, face, or ocular movements (Table 24.2) and the underlying medical or neurologic condition is often thought sufficient to explain the impaired consciousness. NCSE is also under-diagnosed in the elderly, in whom confusion is frequently blamed on other causes such as toxic metabolic disturbances and dementia [89, 90].

EEG Patterns Consistent with NCSE: Salzburg Criteria

Various criteria for which EEG patterns constitute NCSE have been proposed and modified over time [4, 10, 91]. Based on these criteria, an expert panel at the 4th London Innsbruck Colloquium on Acute Seizures in Salzburg, Austria proposed the working criteria for NCSE known as the Salzburg Consensus Criteria for NCSE (SCNC). Primary criteria for NCSE include prolonged epileptiform discharges faster than 2.5 Hz. For patterns 2.5 Hz or slower, but at least 0.5 Hz, there are secondary criteria that must be satisfied to diagnose NCSE: (1) subtle clinical ictal phenomena, (2) typical spatiotemporal evolution of rhythmic and/or epileptiform discharges, or (3) clinical and EEG response to ASD treatment. There is currently no consensus on the minimum duration of an ictal pattern to qualify as NCSE, so the distinction between recurrent NCSzs and NCSE in patients with critical illness or coma can be somewhat arbitrary. Classical coma patterns such as diffuse polymorphic delta activity, spindle coma, alpha/theta coma, low output voltage, or burst–suppression do not represent NCSE.

Treatment

General Considerations

There are currently no randomized studies upon which to base treatment decisions for NCSE, leading to considerable controversy about whether to treat NCSE as aggressively as one treats convulsive SE [92]. In all patients with NCSE, an effort should be made to treat seizures as quickly as possible, but with minimal sedation, to avoid worsening an encephalopathy. The primary goal should be avoidance of harm that can be associated with sedation and intubation, as these risks may be higher than the risk of neuronal injury from NCSE itself. Unfortunately, with the lack of clear data to predict the risk of neuronal injury from NCSE, treatment decisions must ultimately be made on a case-by-case basis.

Table 24.3 Non-pharmacologic critical care management

	Goals	Critical care management
Immediate	Evaluate for airway patency	Noninvasive airway protection – Administer oxygen – Head positioning – Intubate if airway compromised
	Establish and support vital signs	– Oxygen saturation, BP, HR
	Establish medication route	Peripheral IV access (If no IV access can be established, consider IM options detailed in Table 24.4)
Initial	Stop seizures	See Table 24.4
	Support CPP	Vasopressor support of BP if SBP < 90 mmHg or MAP < 70 mmHg
	Evaluate for – New or worsening acute intracranial process – Toxic metabolic disturbance	Neurologic exam Complete blood count, metabolic panel, calcium, ammonia, magnesium, ASD levels, toxicology Neurodiagnostic testing – Head CT – Continuous EEG (if not already initiated)
Ongoing	Additional diagnostic testing Treat infectious/metabolic issues Nutritional support	– Brain MRI – LP for evaluation of infectious and inflammatory/autoimmune causes

Abbreviations: *ASD* anti-seizure drug; *BP* blood pressure; *CPP* cerebral perfusion pressure; *CT* computed tomography; *EEG* electroencephalography; *HR* heart rate; *IM* intramuscular; *IV* intravenous; *LP* lumbar puncture; *MAP* mean arterial pressure; *MRI* magnetic resonance imaging; *SBP* systolic blood pressure

Nevertheless, the Neurocritical Care Society [6] and the European Federation of Neurological Societies [49] have published treatment guidelines recommending that NCSE be treated similar to convulsive SE, but with additional attempts at non-coma-inducing treatment before moving to the use of anesthetic drugs. Initial treatment strategies include simultaneous assessment and management of airway, breathing, circulation (obtain IV access, administer O_2, and secure the airway as needed), abortive ASD treatment, screening for underlying causes including identification of causative drugs, and immediate treatment of life-threatening etiologies (e.g., meningitis, intracranial mass lesions, and hypertensive crisis) (Table 24.3). Importantly, C-EEG monitoring should always be utilized to guide therapy.

Initial Pharmacologic Therapy

Unlike convulsive SE, NCSE is a more heterogeneous diagnostic entity and less amenable to standard treatment algorithms. Treatment must be individualized to the patient, tailored to the perceived urgency and morbidity of the underlying condition.

For the initial treatment of NCSE in adults, a benzodiazepine (lorazepam, diazepam, or midazolam) should be administered intravenously (or intramuscularly if peripheral access is not obtainable) in combination with a non-coma-inducing ASD for maintenance therapy, such as fosphenytoin/phenytoin, valproate, levetiracetam, or lacosamide. Suggested doses are provided in Table 24.4.

Support for the use of benzodiazepines and other ASDs for NCSE is primarily extrapolated from data in patients with GCSE. In clinical trials, the use of benzodiazepines for convulsive SE is associated with shorter seizure duration and a lower risk of cardiorespiratory complications compared with placebo [93]. There are, however, observational data to suggest that overtreatment (defined as using doses >130% of the recommended doses) might be associated with a higher need for intubation [94].

Fosphenytoin/phenytoin is the most commonly used IV ASD for NCSE [95, 96] but several studies indicate that valproate is a good alternative, with equal or better efficacy, as shown in clinical trials of patients with GCSE [96–98]. Levetiracetam is a safe alternative with few side effects and no drug interactions, but clinical trial data for its use in either NCSE or GCSE are lacking, and early evidence suggests it may be less effective than either phenytoin or valproate [99]. Lacosamide is also well tolerated and a promising alternative, but data are still limited. In 2013, a review of published case series utilizing lacosamide for the treatment of all types of SE found it effective in 56% of patients [100]. More recently, the Treatment of Recurrent Electrographic Nonconvulsive Seizures (TRENdS) study aimed to compare IV lacosamide with fosphenytoin for treatment of nonconvulsive seizures not meeting criteria for SE (defined as less than 30 min of electrographic seizure activity per 1 h of C-EEG

Table 24.4 Pharmacotherapy for nonconvulsive status epilepticus

Drug	Initial dose	Follow-up dose		Side effects	Considerations
		Reloading dose	Maintenance dose		
Initial—Benzodiazepines					
Use for early abortive therapy while first-line non-sedating IV ASD is loaded					
Lorazepam	2–4 mg IV	Repeat 2–4 mg q 2 min up to 0.1 mg/kg	N/A	Hypotension, respiratory depression	Low lipid solubility thus no significant redistribution (longer anti-seizure effect)
Diazepam	10 mg IV	Repeat 10 mg IV	N/A	Hypotension, respiratory depression	Highly lipid soluble thus rapid redistribution (short acting, may require multiple dosages)
Midazolam	10 mg IM	Repeat 10 mg IM	N/A	Hypotension, respiratory depression	Renal elimination, rapid redistribution (short acting)
Early—First-line non-sedating anti-seizure drugs (ASDs)					
Phenytoin	20 PE/kg, at up to 50 mg/min	5–10 mg/kg	5–7 mg/kg/d divided every 8 h	Hypotension, arrhythmia, soft tissue/venous irritation at IV site	Only compatible in saline
Fosphenytoin	20 PE/kg, at up to 150 mg PE/min	5–10 mg PE/kg	5–7 mg PE/kg/d divided every 8 h	Hypotension, arrhythmia	Compatible in saline, dextrose and lactated ringers solutions
Valproate	20–40 mg/kg, at 3–6 mg/kg/min	20 mg/kg	30–60 mg/kg/d, divided every 6 h	Hepatotoxocity, hyperammonemia, pancreatitis, thrombocytopenia	Teratogenicity
Levetiracetam	1500–2000 mg over 15 min	1000–2000 mg	1–5 g/d divided every 12 h	Behavioral, mood change	Minimal drug interactions, not hepatically metabolized
Lacosamide	400 mg over 15 min	200 mg	400–600 mg/d divided every 12 h	PR prolongation, hypotension	Minimal drug interactions
Second-Line—Non-sedating ASDs (if already intubated, skip to sedative/anesthetics)					
If initial non-sedating ASD is ineffective, then choose the next ASD from the list above					
If no IV access, the following can be given orally, Mainly adjunctive role					
Topiramate	100 mg every 12 h	N/A	Up to 800 mg/d divided every 12 h	Metabolic acidosis	May be given rectally
Pregabalin	75 mg every 12 h	N/A	Up to 600 mg/d divided every 12 h		Few drug interactions
Late—Sedative/anesthetics					
		Continuous infusion dosing—titrate to EEG			
Midazolam	0.2 mg/kg at 2 mg/min	0.05–2 mg/kg/h Rebolus 0.1–0.2 mg/kg and increase rate by 0.05–0.1 mg/kg/h every 3–4 h		Hypotension Respiratory depression	Tachyphylaxis occurs after prolonged use

(continued)

Table 24.4 (continued)

Drug	Initial dose	Follow-up dose		Side effects	Considerations
		Reloading dose	Maintenance dose		
Propofol	1–2 mg/kg loading dose then 20 mg/kg/min	30–200 mcg/kg/min Use caution with high doses (>80 mcg/kg/min) for extended periods of time Rebolus 1 mg/kg and increase rate by 5–10 mcg/kg/min every 5 min		Hypotension Respiratory depression Propofol infusion syndrome Hypertriglyceridemia	Must adjust daily caloric intake (1.1 kcal/ml)
Phenobarbital	20 mg/kg at 50–100 mg/min	Additional 5–10 mg/kg bolus to achieve serum level >30		Hypotension Respiratory depression	Prolonged half life
Pentobarbital	5–15 mg/kg up to 50 mg/min	0.5–5 mg/kg/h Rebolus 5 mg/kg and increase rate by 0.5–1 mg/kg/h every 12 h		Hypotension Respiratory depression	Potential for paralytic ileus and cardiac depression
Thiopental	2–7 mg/kg at 50 mg/min	0.5–5 mg/kg/h Rebolus 1–2 mg/kg and increase rate by 0.5–1 mg/kg/h every 12 h		Hypotension Respiratory depression Cardiac depression	Metabolized to pentobarbital
Ketamine	3 mg/kg over 15 min	1.0–7.5 mg/kg/h		Hypertension Hallucinations Increased ICP	Adjust total volume for fluid-restricted patients

IV intravenous
ICP intracranial pressure
N/A not available

monitoring) [101]. Patients were randomized to treatment with a loading dose of lacosamide (400 mg) or fosphenytoin (20 mg/kg), with rebolus of the ASD if breakthrough seizures occurred within 8 h of the initial bolus. Control of seizures for 24 h was considered successful treatment. Of the 62 patients who completed the study, 63% receiving lacosamide became seizure-free compared to 50% treated with fosphenytoin, indicating that lacosamide and fosphenytoin were essentially equally efficacious.

Treatment of Refractory Nonconvulsive Status Epilepticus

Refractory status epilepticus (RSE) refers to SE that continues despite administration of therapeutic doses of a benzodiazepine as well as a traditional ASD. At this stage, treatment of GCSE typically involves anesthetic agents, but there are few data exploring the use of anesthetic agents for refractory GCSE, let alone for NCSE. The most commonly utilized agents include propofol and midazolam due to their widespread availability and relative safety margin, although both agents commonly produce hypotension. In addition, prolonged use of propofol has been associated with the "propofol infusion syndrome" which includes metabolic acidosis, renal failure, and rhabdomyolysis, and can be fatal. Barbiturates (pentobarbital, phenobarbital, thiopental) are also a consideration at this stage, particularly when midazolam and propofol are ineffective. The advantages of barbiturates include fewer breakthrough seizures, but often at the risk of more significant hypotension, and a longer half-life can lead to prolonged ICU stays [102]. Finally, ketamine is a nontraditional anesthetic option with a novel mechanism of action (of NMDA receptor antagonism) and a low incidence of hypotension. In a retrospective case series of 60 episodes of RSE (68% of which is NCSE), ketamine appeared to contribute to control of SE in 32%, including in 12% when it was the last drug added [76].

Aside from anesthetic agents, administration of oral ASDs that can be titrated relatively rapidly such as topiramate, pregabalin, clobazam, and perampanel may also be of some value when benzodiazepines and traditional intravenous ASDs fail, but evidence for these treatments is limited to smaller uncontrolled case series.

In patients treated with continuous infusions, seizures should be stopped for a minimum of 12–24 h before beginning anesthetic taper, typically over an additional 24 h period. If seizures recurred with a prior taper, it may be necessary to treat longer and taper more slowly the next time, while maintaining high therapeutic levels of traditional ASDs. If SE continues or recurs 24 h after the onset of anesthetic therapy (including cases that recur on the reduction or withdrawal of anesthesia), the patient is said to have entered a stage of super-refractory SE (SRSE), which is discussed in detail in Chapter 17, "Treatment of Refractory and Super-Refractory Status Epilepticus."

How Aggressively Should One Treat Nonconvulsive Status Epilepticus? The Current Evidence

Whether patients benefit from aggressive treatment of NCSE, or even brief NCSzs, is currently unknown [3, 92]. Furthermore, it is not always clear in the critically ill patient whether worsening neurologic status indicates damage from electrographic seizures themselves, or whether the EEG findings of electrographic seizures are simply a marker of worsening neurologic status from the primary neurologic injury. Multiple observational studies in adults and children, however, have found that NCSE and NCSzs are independent predictors of poor outcome, worse quality of life [3, 52–55, 75, 76], and development of epilepsy [103, 104]. In addition, seizure duration and delay in diagnosis have been associated with higher mortality. There is also evidence that those with a greater seizure burden have a greater chance of neurologic decline [38].

Animal data suggest that NCSE superimposed on acute brain injury is injurious to neurons [5, 105]. There are also data in humans to support consideration of aggressive therapy. Specifically, NCSzs after ICH have been associated with worsening NIH Stroke Score and increase in midline shift [48, 49], while NCSzs after SAH may contribute to transient brain hypoxia and increased intracranial pressure [106]. Studies in patients with traumatic brain injury suggest that these patients may be more susceptible to injury from seizures, as evidenced by elevations in intracranial pressure as well as markers of neuronal injury [48, 107–109]. Furthermore, NCSzs have been associated with elevated neuron specific enolase (NSE), a key enzyme for energy metabolism and a marker of acute brain injury and damage to the blood–brain barrier [110]. In addition, NSE levels have been correlated with the duration of SE, suggesting that early treatment of NCSzs may be beneficial [110].

Specific examples of situations that may warrant aggressive therapy and anesthetic induced coma include (1) subtle SE developing from generalized convulsive seizures, which has been associated consistently with poor outcome [31, 111], and (2) NCSE in patients with acute brain injury, which can lead to secondary neuronal injury, as evidenced by an increase in intracranial pressure, midline shift, and elevated lactate–pyruvate ratios [48, 49, 106]. Optimal management, however, may vary considerably in specific circumstances. For example, NCSE in post-operative patients or patients with significant traumatic brain injury who are already mechanically ventilated are more likely to be managed with immediate anesthesia. On the other hand, patients with prior epilepsy and NCSE brought about by ASD nonadherence or withdrawal should be treated with immediate reinstatement of the withdrawn ASDs (parenterally if possible).

The argument against aggressive treatment of some forms of NCSE is based primarily on observations that the prognosis of patients with NCSE depends largely on factors other than seizure control, of which etiology and age are the most important [112–115]. One retrospective study compared critically ill older patients with NCSE treated aggressively with IV benzodiazepines in an ICU with those treated less aggressively outside of the ICU because their advance directives mandated avoidance of aggressive care [113]. Use of IV benzodiazepines was associated with prolonged hospitalization and increased mortality despite similar severity of illness.

For NCSE patients who are not intubated, or intubated but hemodynamically unstable, starting with a conventional, parenteral ASD may avoid respiratory depression and hypotension that can result in a prolonged hospital stay. Based on the EEG response, a second ASD can be considered if electrographic improvement is not achieved. For intubated patients with stable blood pressure, the use of more aggressive treatment with IV anesthetics increases the risk of hypotension and respiratory compromise but provides a greater chance of a rapid and effective cessation of seizure activity in order to prevent secondary neuronal injury. Physicians must balance the potential morbidity associated with NCSE and that induced by IV-ASDs and anesthetics. In all cases, the treatment goal should be to achieve clinical improvement and avoid medication-induced effects that could worsen prognosis.

The Ictal–Interictal Continuum

In critically ill patients, there are frequently complex periodic and rhythmic electrographic patterns that do not meet definitive criteria for an ictal (i.e., epileptic seizure) pattern but rather lie along a spectrum commonly referred to as the "ictal–interictal continuum" (IIC) [3, 116]. In some clinical scenarios the occurrence of an IIC pattern can be highly suspicious for ictal activity [4, 116] and hence a discussion of these rhythmic and periodic patterns and consequent treatment decisions is necessary. The Standardized Critical Care EEG Terminology published by the American Clinical Neurophysiology Society (ACNS) [91, 117] describes these patterns that are said to fall along the IIC, which include lateralized rhythmic delta activity (LRDA) and generalized and lateralized periodic discharges (GPDs and LPDs). These patterns can also be induced by alerting stimuli, in which case they are referred to as stimulus-induced rhythmic, periodic, or ictal discharges (SIRPIDs) [118]—which introduces an additional dilemma regarding the pathophysiology and clinical significance of the pattern. Importantly, additional terminology to describe the frequency of each pattern and appearance of any additional fast, rhythmic, or 'spiky'

Table 24.5 Complications of nonconvulsive status epilepticus

Medication specific
– Propofol: Propofol-related infusion syndrome (PRIS), triglyceridemia – Barbiturates: Paralytic ileus, propylene glycol toxicity, lingual edema – Valproate: hyperammonemia, platelet dysfunction – Phenytoin/fosphenytoin: Cardiac arrhythmia – Lacosamide: PR prolongation, angioedema
Complications of prolonged ICU stay
Pulmonary – Recurrent mucous plugging – Hospital acquired pneumonia – Atelectasis – Tracheostomy
Infectious – Catheter-associated urinary tract infection – Sepsis – Pseudomembraneous colitis
Integumentary – Skin breakdown, including scalp in case of prolonged use of C-EEG
Venous thromboembolic disease – Pulmonary embolus – Deep vein thrombosis
ICU-acquired weakness – Critical illness myopathy – Critical illness neuropathy
Neuropathologic: – Hippocampal atrophy (in patients with nonconvulsive seizures after TBI)

PR PR interval in electrocardiography, or time from the onset of the P wave to the start of the QRS complex
C-EEG continuous electroencephalography
TBI traumatic brain injury

activity are important modifiers that can influence the risk of associated seizures and therefore, treatment decisions.

A practical approach to EEG patterns that fall along the IIC includes taking into account associated clinical symptoms, response to the administration of a benzodiazepine or other rapidly acting ASDs, and the presence of corresponding imaging findings or biomarkers of neuronal injury.

In the absence of a clear epileptic clinical correlate, the appropriate decision is often to watch the EEG recording to look for changes that are more definitive of an ictal pattern or to proceed with a benzodiazepine (BZD) trial [111]. Unfortunately, BZD trials are often equivocal and can be confounded by the fact that most patients have altered level of consciousness at baseline and the use of a high-dose BZD will invariably induce further sedation. The test should only be considered positive if there is a normalization of the EEG background *and* the patient improves clinically. If the BZD trial is negative or equivocal and there is still strong suspicion of a potentially ictal pattern, a trial of a conventional ASDs with rapid titration is often employed. Still, clinical improvement in ICU patients is often gradual or delayed, so it is recommended to allow at least a 24 h observation period while keeping adequate maintenance doses of ASDs before declaring the ASD trial negative.

When BZD and ASD trials are equivocal, imaging studies and biochemical markers in serum or cerebrospinal fluid can be used to suggest whether the suspicious pattern is inducing neuronal injury, but these biochemical markers (and functional neuroimaging techniques) are expensive technology not routinely available even in some large academic institutions. In their absence, we recommend continued C-EEG monitoring for at least 24 h to assess for any change in the pattern that would necessitate treatment.

Complications of Treatment

Systemic complications can be a direct consequence of ASDs or a result of prolonged immobility and ICU stays (Table 24.5). Multiple organ systems can be affected and add to cumulative morbidity and mortality. Awareness and heightened surveillance is required to prevent hospital-acquired pneumonias, catheter-associated infections, thromboembolic disease, and skin breakdown. Multiple markers of systemic injury have been independently associated with mortality in SE. Therefore, screening for abnormalities in serum lactate, arterial blood gas, creatine kinase, cardiac troponins, electrocardiogram, and chest

X-ray is recommended. In addition to medical complications, there is also evidence that NCSzs in patients with traumatic brain injury can result in bilateral hippocampal atrophy [71]. Close attention to these treatment-related complications of SE is indispensable and may impact outcome favorably [119].

Conclusion

The frequency of nonconvulsive status epilepticus was largely unrecognized until the use of C-EEG monitoring demonstrated it to be relatively frequent in a variety of hospital settings. There is no official classification system, but numerous subtypes and presentations exist, which can make diagnosis elusive. In the critically ill, acute brain injuries such as subarachnoid hemorrhage, traumatic brain injury, stroke, and anoxic brain injury are common underlying causes. Impairment of consciousness is a ubiquitous symptom of NCSE and can range from mild confusion to coma, while subtle movements such as nystagmus, eye deviation, or hippus are suggestive but not sensitive for the diagnosis. In the critically ill, EEG findings include a range of periodic or rhythmic discharges which may or may not meet criteria for electrographic seizures, making accurate diagnosis challenging. NCSE is poorly replicated by available animal models, and there is a lack of randomized treatment trials, which means that standardized treatment guidelines do not exist. Whether NCSE should be treated as aggressively as convulsive SE remains controversial. Nevertheless, a concerted effort should be made to diagnose and treat NCSE as quickly as possible, but with minimal sedation to avoid prolonged hospital stays. Typical treatment strategies involve initial use of benzodiazepines followed by a non-sedating ASD that can be administered intravenously. If initial treatment fails, judicious decision-making is required in order to weigh the risk of aggressive treatment against the hazards of ongoing seizures in the context of the overall clinical prognosis.

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Consequences of Nonconvulsive Status Epilepticus: Experimental and Clinical Evidence

25

Karthik Rajasekaran and Howard P. Goodkin

"*Data! Data! Data!" he cried impatiently. "I can't make bricks without clay*".
Sir Arthur Conan Doyle, *The Adventure of the Copper Beeches.*

Introduction

Axis I of the recently updated International League Against Epilepsy (ILAE) classification of status epilepticus (SE) [1] divides SE into two forms: convulsive SE and nonconvulsive SE. Nonconvulsive SE (NCSE), i.e., prolonged self-sustaining seizures without prominent motor activity, is further subdivided into *NCSE with coma* and *NCSE without coma*. NCSE without coma includes both generalized (e.g., typical absence SE) and focal (e.g., NCSE with impaired consciousness, previously known as complex partial SE, CPSE) types.

The predominant feature of the majority of NCSE episodes is an ictal alteration of mental status characterized as lethargy, hallucinations, confusion, mood disturbances, bizarre behavior, or coma. A review of the semiologic description of 105 episodes of SE in the literature found that an alteration of mental status was present in 82% of those episodes [2]. Episodes in which the patient's consciousness is preserved in the absence of prominent motor symptoms would be classified as focal NCSE without impaired awareness, previously known as simple partial SE. During a prolonged seizure of NCSE, motor manifestations may not be prominent, but subtle head and eye deviation, twitching movements, and myoclonia may be observed. Further, autonomic manifestations such as changes in heart rate and blood pressure may occur.

The ILAE definition of SE [1] includes two time points, t1 and t2. t1 represents when treatment should be initiated because after this time point the probability that the seizure will terminate without intervention is low. t2 is defined as the time point at which long-term consequences resulting from the episode of SE may occur. For generalized tonic-clonic SE, these time points are defined as t1 = 5 min and t2 = 30 min. Although t1 (10 min) and t2 (>60 min) values are provided for focal SE with impaired awareness, and an estimated t1 (10–15 min) value is provided for absence SE, the ILAE Task Force on Classification of Status Epilepticus noted that evidence in support of these values (or indeed, those for all forms of NCSE), are lacking and that additional studies are needed to begin to define these time points better.

The exact incidence of all forms of NCSE is not known and depends on the population studied, the setting, and the operational duration used to define an episode of NCSE [3, 4]. It is also clear that the era during which the study was performed is important, as the introduction of, and increasing use of, portable continuous electroencephalography (CEEG) technology in emergency departments and intensive care units has resulted in a greater recognition of NCSE [4, 5].

Recognition of NCSE often requires heightened clinical suspicion. NCSE can be preceded by a convulsive seizure that evolves to a stage of electromechanical dissociation, the so-called *subtle status epilepticus* [6], but frequently it occurs without an earlier convulsive seizure. In the emergency department and critical care settings, an alteration of mental status unresponsive to appropriate therapy for the underlying medical condition should lead to the use of EEG to evaluate for the possibility of NCSE [4].

Further discussion of the evaluation and treatment of NCSE are beyond the scope of this chapter. The primary question to be addressed here is one of prognosis: Does NCSE with coma, as observed in the critical care setting, lead directly to neuronal injury or change in neuronal function? The answer to this question may assist in optimizing management of this condition [7], especially given recent concerns that a higher risk of mortality is associated

H.P. Goodkin (✉)
Departments of Neurology and Pediatrics, University of Virginia, 800394, Charlottesville, VA 22908, USA
e-mail: HPG9V@hscmail.mcc.virginia.edu

K. Rajasekaran
Neurology & Neurotherapeutics, University of Texas Southwestern Medical Center, 8813, 5323 Harry Hines Blvd, Dallas, TX 75390, USA
e-mail: Karthik.Rajasekaran@UTSouthwestern.edu

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with the administration of anesthetic therapies [8–14]. The significant challenge of integrating evidence from heterogeneous preclinical and clinical studies has caused considerable debate on whether this form, or indeed any form, of NCSE has direct negative consequences for brain function, or whether the NCSE itself is a consequence of the primary insult and without its own independent influence on prognosis [15–17]. It has long been assumed that outcomes of NCSE are etiology-dependent rather than due to the NCSE per se. Hence, the current consensus is that the prognosis of NCSE with coma is typically worse in patients with acute neurologic illnesses compared to that in patients with prior epilepsy [18–20].

Consequences of Nonconvulsive Status Epilepticus: Preclinical Animal Models

Studies investigating the mechanisms and negative consequences of prolonged seizures and mechanisms of epileptogenesis have long depended on preclinical animal models in which seizures are induced in naïve animals using a chemoconvulsant such as the anticholinergic agent pilocarpine, electrical stimulation, or hyperthermia. Although this induction frequently induces a convulsive seizure, several of the induction techniques have been modified to induce prolonged seizures without a major motor component.

Several of these preclinical models replicate key features of absence SE [21–23] or CPSE [24–27]. A model for NCSE in the critically ill, however, is still lacking. Despite this absence, a review of the preclinical literature is instructive when considering the question of the consequences of NCSE in this population as there are several examples in which it has been demonstrated that prolonged seizures, not accompanied by convulsive movements or secondary systemic changes (hyperpyrexia, lactic acidosis, hypotension, hypoxia, and hypoglycemia), are capable of producing neuronal injury.

The classic example of this finding was a study performed by Meldrum and colleagues [28] in which seizures were induced using the GABA antagonist bicuculline in paralyzed, artificially ventilated baboons. In these animals, with minimal secondary physiologic changes (e.g., a mild increase in temperature and slight decrease in arterial oxygen tension in several of the animals), ischemic neuronal injury was observed in the neocortex, thalamus, and hippocampus, in several animals in which the seizure lasted longer than approx. 3.5 h [28, 29]. An important observation was that while injury was present, it was to a lesser degree than that observed following convulsions in the same model [29], suggesting that the neuronal injury was the result of *both* the prolonged, recurrent neuronal activation that occurs during the seizure and the secondary systemic changes that occur in response to the seizure.

This finding in the paralyzed, ventilated baboon was subsequently confirmed by Nevander and colleagues using a flurothyl-induced model of SE in ventilated and well-oxygenated rats [30]. Histologic studies completed 1 week after prolonged seizures of 15–120 min or longer showed seizure duration-dependent neuropathologic changes —including infarction of the substantia nigra and *pars reticulata* following SE for 30 min. After 45–120 min of seizures, damage was observed in layers 3 and 4 of the neocortex. Seizure duration of 60–120 min resulted in neuronal damage that extended to the amygdala, thalamus, and hippocampal CA4 and CA1 regions. Interestingly, CA3 and dentate granule cells remained unaffected. For seizure duration beyond 120 min, there was damage in both the neocortex and ventral posterior thalamic nuclei, together with evidence of neuronal necrosis at sites close to the ventricles.

A limitation of studies in which prolonged seizures are induced using a systemic chemoconvulsant is the potential that the injury is a direct result of the chemoconvulsant and not the seizure. Electrical stimulation to induce the seizure avoids this limitation of chemoconvulsants, and there are several examples in which prolonged electrical stimulation in the absence of convulsive seizures was correlated with neuronal injury. For example, Sloviter and colleagues performed electrical stimulation of the angular bundle of the perforant pathway in adult rats for a period of 24 h [25]. During the stimulation, the animals were anesthetized, and although occasional wet dog shakes (automatisms resulting from activation of the dentate gyrus) were observed, convulsions did not occur. Histologic examination showed extensive dorsal hippocampal damage on the stimulated side, including in the hilar interneurons in the dentate gyrus and CA3 and CA1 pyramidal neurons.

Similarly, Thompson, Wasterlain and colleagues [26] demonstrated that prolonged focal electrical stimulation in young animals resulted in neuronal death. Focal NCSE was induced in developing animals (postnatal day 14–15—which approximates the brain development of a human toddler) by stimulating the perforant pathway for 16 h. During the stimulation, the animals exhibited wet dog shakes and hind limb scratching. Forelimb clonic movements were observed only rarely. The day after stimulation, there was significant necrotic death of interneurons in the hilar region and of pyramidal cells in the CA1 and CA3 regions of the hippocampus ipsilateral to stimulation. This necrotic cell death was also present in the contralateral CA1 and CA3 regions and extended to the ipsilateral and contralateral subiculum and prepiriform cortex.

Brandt, Löscher and colleagues [27] electrically stimulated the basolateral amygdala to induce prolonged focal nonconvulsive seizures, focal nonconvulsive seizures

intermittently interrupted by generalized convulsive seizures, and prolonged generalized convulsive seizures. Histologic studies performed 48 h after NCSE showed that in animals with NCSE lasting longer than 1 h, ipsilateral neurodegeneration was apparent in many regions, including in the amygdala, piriform cortex, entorhinal cortex, endopiriform nucleus, and mediodorsal thalamus, whereas no damage was found in the hippocampus or substantia nigra. As in the studies of Meldrum and colleagues reviewed above, the injury in NCSE was more restricted and less severe than that found when convulsive seizures were observed. Further, although there was a high probability (90%) of developing chronic epilepsy in those animals with convulsive seizures, about 30% of the animals in the focal NCSE group developed chronic epilepsy. Although the electrically induced focal NCSE that occurred in this study and in that of Thompson and colleagues [26] are more directly comparable to CPSE than to focal NCSE in critically ill patients (in whom the episode of NCSE occurs in the setting of traumatic brain injury, subdural hemorrhage, or stroke), these findings raise concern that prolonged excessive neuronal activity in a focal region of the brain has the capacity to directly induce cell death.

A focal preclinical model that may be considered a better reflection of central nervous system consequences of nonconvulsive seizures in the critically ill is one in which nonconvulsive seizures were induced by an ischemic injury resulting from either permanent or transient (2 h) occlusion of the right middle cerebral artery (MCA) in adult rats [31]. In this model, the nonconvulsive seizure begins over the ischemic right hemisphere and may then spread to involve the nonischemic left hemisphere. The seizures lasted on average 60 s, and recurred on average 10 times, in the first two hours of occlusion. The seizures were accompanied by periodic discharges and intermittent EEG rhythmic activity that commenced at approximately 1 h after the occlusion and continued for up to the next 72 h. Studies using this model provided confirmatory evidence that nonconvulsive seizures per se following MCA occlusion contribute to neuronal injury and functional morbidity. The authors found that treatment with antiseizure drugs, either immediately before or within 30 min of MCA occlusion, reduced the incidence of seizures after stroke. Importantly, the reduction in seizures was correlated with reduced brain infarct volume and mortality and improved neurologic recovery [32, 33].

Consequences of Nonconvulsive Status Epilepticus: Clinical Studies

Norbert Weiner, often credited as the father of Cybernetics (i.e., systems theory), is frequently quoted as having said, "the best material model of a cat is another, or preferably the same, cat." The preclinical models reviewed to this point demonstrate that persistent abnormal neuronal activity may result in neuronal death in the absence of convulsive movements. It is fully appreciated, however, that focal limbic SE, with or without secondarily generalized convulsive seizures, in the freely moving or paralyzed, ventilated animal as induced by either a chemoconvulsant or electrical stimulation, may not be the best model for the *cat of interest*, which is NCSE in the critically ill patient. Therefore, it is important to review those studies performed in the '*same cat*,' i.e., human patients.

The literature is replete with examples demonstrating that critically ill children and adults with nonconvulsive seizures and NCSE are at higher risk for morbidity and mortality [34–48]. Many of these studies suggest that outcome is strongly influenced by the underlying etiology rather than by the NCSE per se [18, 49–58].

Despite this association of underlying etiology with outcome, several recent studies suggest that the NCSE itself may also directly negatively affect outcome. For example, Payne and colleagues [59] rigorously addressed the relationship of electrographic seizures to declining neurologic function. They prospectively studied continuous video-EEG records (21–56 h) of 259 critically ill children (ages 0.3–9.7 years) and found that electrographic seizures occurred in 93 of the children (36%), of whom a third had a prior diagnosis of epilepsy: 14% of the subjects with seizures had exclusively convulsive seizures, 47% a combination of convulsive and nonconvulsive seizures, and 40% exclusively nonconvulsive seizures. Among these children, electrographic SE was found in 23 (9% of the entire study population). Among all subjects, 67% had a neurologic decline (from the time of admission) by at least 1 point on the pediatric cerebral performance category (PCPC) scale. Most importantly, for the question of whether NCSE worsens prognosis, the study showed that an increased electrographic 'seizure burden,' greater than 20% per hour (i.e., >12 min of seizure activity per hour), significantly accelerated neurologic decline and worsened PCPC scores (although without an impact on mortality). Children with PCPC worsening had a mean seizure burden of 15.7% versus 1.8% for those without PCPC worsening. Seizure duration was independently associated with neurologic decline regardless of the diagnostic category, although subjects with systemic diseases and acute seizures appeared to fare worse. This study provided evidence that electrographic *seizure burden* per se *is strongly associated with increased morbidity in critically ill children*, implying the need for aggressive antiseizure drug therapy. Still, as 80% of the children in this study received antiseizure drugs before and during EEG monitoring without a change in the association between seizure burden and neurologic outcomes as determined by the PCPC scale, it remains an open question whether earlier and more

aggressive treatment, including the use of more sedating agents, could improve outcomes [43, 60].

While the study by Payne and colleagues looked at short-term outcome, Abend and colleagues [42] reported the long-term outcomes in children admitted to the Pediatric ICU and diagnosed with NCSE. At after-discharge follow-up (median duration 2.6 years) for 60 children, they found that NCSE (but not isolated electrographic seizures) in children with previously normal developmental baselines was associated with an unfavorable developmental outcome, including decreased quality of life. Only 13% of children with NCSE had a favorable outcome whereas 64% of the subjects who did not have seizures (or had isolated electrographic seizures, but not SE) had a relatively favorable developmental outcome and PCPC scores. Further, among children without a prior history of epilepsy, having electrographic SE was associated with an increased risk for the development of epilepsy (69%) compared to the risk for those who had isolated electrographic seizures (38%) or no seizures (21%), consistent with earlier data [61]. The study was expanded to assess neurobehavioral outcomes in a smaller cohort measuring adaptive and daily skills, emotional problems, competencies, and real-world behavioral manifestation of executive skills. Patients with NCSE (32 patients; age range: 2.0–9.8 years) had worse adaptive behavior compared to those with no seizures. There was also a trend toward worse behavioral-emotional and executive skills, but the smaller sample size probably precluded statistical significance. Interestingly, in this expanded study, the authors did not find significant differences in worsened outcomes between patients with 'electrical seizures' and 'electrical SE' (the terminology adopted in the studies). This finding may be the result of inadequate seizure burden stratification in the study, as NCSE can involve multiple brief seizures rather than just a single prolonged seizure. While this caveat means that we still do not know whether the negative outcomes are due to seizures per se or their underlying triggers, the data suggest the need for expeditious treatment of electrographic seizures and the potential for NCSE per se to at least contribute to or exacerbate poor outcomes.

In adults, Punia and colleagues [62] retrospectively studied 1163 consecutive patients admitted to the ICU who had CEEG monitoring. Of the 200 patients they detected having periodic lateralized epileptiform discharges (PLEDs) or nonconvulsive seizures or both on the EEG, they obtained follow-up on 118 patients. The predominant etiologies in these patients were stroke (28%), hemorrhage (26%), and tumor (14%). They found that 24% of patients in the PLEDs-only group had seizure recurrence after discharge and, even after excluding those with a prior history of epilepsy, patients who had nonconvulsive seizures in the ICU (with or without PLEDs) had a 5 times greater likelihood of seizure recurrence than those with PLEDs alone [63].

Recently, Claassen and colleagues [64] reported the relationship between seizure burden, as defined by duration of seizures on CEEG, and functional and cognitive outcomes 3 months after subarachnoid hemorrhage (SAH). They studied the records of 420 SAH patients admitted from 1996 to 2013 who underwent CEEG for an average duration of 96 h. They found that 50 patients (12%) had seizures on EEG, including NCSE in 46 patients (92%) and nonconvulsive seizures in 4 (8%). NCSE had an average duration of 6 h. At 3 months, 178 patients (58%) were either dead or disabled and, after adjusting for other predictors of outcome, seizures were associated with a threefold greater probability of worsened functional outcome (modified Rankin Scale) compared to that for patients without seizures. Among patients with seizures, the magnitude of association of NCSE to poorer outcomes was stronger. Importantly, the authors found a direct association of seizure burden to negative functional outcome. Every additional hour of NCSE was associated with a 10% greater likelihood of functional disability or death at 3 months. Cognitive outcomes were measured by telephone interview (TICS, a scale that ranges from 0 to 51) 3 months after SAH in a third of the patients (121), of whom 11 (9.1%) had had at least one seizure on the CEEG. Although nonconvulsive seizures were not independently associated with worsened cognitive outcome, seizure burden was, as there was a small but measurable decrease of 0.19 points (95% CI −0.33 to −0.05) in the TIC score for every 1 h of seizure activity. Overall, the study demonstrated that both nonconvulsive seizures and NCSE result in poorer functional outcomes with increasing seizure burden, independently worsening cognitive outcome.

In a prospective CEEG monitoring study of 140 patients with severe to mild TBI, Vespa and colleagues [65] found that about 23% (32/140) of patients had nonconvulsive seizures, including 4 with NCSE. When 6 of these patients were compared with an age-, sex- and Glasgow coma scale-matched 'control' group of 10 TBI patients who did not have seizures on CEEG, serial MRI scans showed that patients who had nonconvulsive seizures developed hippocampal atrophy, with selectively more significant ipsilateral atrophy and to a lesser extent, contralaterally, without a change in global brain atrophy. In contrast, 'control' TBI patients who did not have seizures did not have hippocampal atrophy. This study suggests that nonconvulsive seizures in TBI patients have additive or synergistic neuropathologic consequences, at least in the hippocampus.

Neuroinflammation frequently accompanies acute brain injuries, and accumulating evidence suggests that inflammation is capable of triggering nonconvulsive seizures, or

NCSE. In a retrospective review of 154 patients in a surgical ICU who underwent CEEG for altered mental status, Kurtz and colleagues [66] found that 29% exhibited periodic epileptiform discharges, 16% had nonconvulsive seizures, and 5% NCSE. Significantly, all patients with NCSE had sepsis. The trigger role for neuroinflammation in inducing nonconvulsive seizures was confirmed in a recent prospective observational study by Claassen and colleagues [67] who followed 479 patients with aneurysmal SAH. Patients were monitored on CEEG from Day 4 through Day 9 following SAH and were treated prophylactically with phenytoin for the first week following SAH. Serum markers of inflammation were measured at various times. Of these patients (average age = 56 years, predominantly women), 11% developed nonconvulsive seizures following SAH (median time: 8.5 days post-SAH). Further, about 8–22% of SAH patients developed infectious complications, including systemic inflammatory response syndrome (SIRS: elevated heart and respiratory rate, high or low body temperature, and serum white blood cell count), and about 20% developed ischemia due to SAH-associated vasospasm. SIRS burden (defined as the mean of daily SIRS scores, as well as the slope of the SIRS curve) was associated with increased infections, including sepsis (19%), pneumonia (54%), UTI (39%) and ventriculitis (31%). Significantly, the authors found that the SIRS burden within 4 days post-SAH was an independent predictor of in-hospital nonconvulsive seizures, after controlling for known predictors and other variables including age, gender, Hunt and Hess grade, aneurysm size, and aneurysm clipping. A SIRS rating of 3 and above was more likely in the 24 h preceding the onset of nonconvulsive seizures. The increase in SIRS rating also corresponded with an increase in the serum levels of inflammatory biomarkers, including TNF-R1 and high sensitivity C-reactive protein. The association between the inflammatory biomarkers and nonconvulsive seizures was especially significant in patients whose EEG had mild or no background attenuation. Most importantly, the authors found that nonconvulsive seizures mediate the effect of SIRS, hsCRP, and TNF-R1 on poor functional outcome at 3 months (as assessed by Rankin scale) suggesting that SAH-associated inflammation leads to nonconvulsive seizures, worsening neurologic outcome. These findings suggest that proactively managing potential neuroinflammation following acute brain injury or systemic infections might prevent the development of nonconvulsive seizures or NCSE in a significant subset of patients.

Conclusions

The available clinical evidence suggests that the outcomes of NCSE are predominantly associated with the etiology [4, 68, 69], but data on long-term follow-up are insufficient to confirm definitively the extent of the functional impact of prolonged NCSE. Aided by increasing CEEG use, emerging evidence in the past 5–7 years suggests the worrying possibility that NCSE is not always a mere harbinger of the severity of the overall condition (neurologic or otherwise) but rather, complicates and also potentially independently impacts outcome. Though animal models have an inherent etiologic bias that is difficult to overcome in determining causality, experimental evidence suggests clearly that prolonged NCSE is associated with neuronal injury impacting functional outcome. As preclinical models of NCSE in the critically ill develop, they will be useful to determine whether (1) the cellular and molecular mechanisms that lead to NCSE are the same as or different from those that lead to convulsive SE and also, (2) whether the neuronal networks recruited during NCSE are the same as or different from those recruited during convulsive SE. Overall, the evidence thus far emphasizes the need for more preclinical studies and for prospective clinical studies of long-term outcome of NCSE, and it recommends the early and widespread use of CEEG to help provide definitive answers to settle the debate: Do the direct consequences of NCSE warrant the risks of the possible untoward effects of heavily sedating antiseizure drugs?

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Status Epilepticus in Neonates

26

Réjean M. Guerriero and Tobias Loddenkemper

Introduction

Seizures are a common feature of neurologic illness in the neonatal period, the first 28 days of life. Neonatal seizures and status epilepticus may occur due to a range of etiologies, including structural injuries, genetic abnormalities, inborn errors of metabolism, and treatable systemic conditions, such as hypoglycemia, among others. In this chapter, we outline unique features of neonatal status epilepticus, including developmental differences in the gamma-aminobutyric acid (GABA) system, as well as the clinical and electrographic presentation, treatment, and outcomes.

Definition

Defining neonatal status epilepticus (SE) remains difficult. Many infants have prolonged seizures on presentation and frequently present with repetitive seizures. Determining whether there is return to baseline, a key component of the SE definition in children and adults, is complicated by differences in age-related responsiveness and by prematurity, critical illness, and encephalopathy.

Neonatal seizures have been defined as having a distinct beginning, evolution of at least 2 microvolts, and a duration of at least 10 s [1, 2]. Defining this beginning, evolution, and end is critical because many neonatal seizures are subclinical or have only subtle clinical features. Distinguishing these features from other types of short, nonevolving rhythmic discharges may prevent overtreatment [3]. The definition of neonatal SE has pitfalls. Typical definitions of SE rely on clinical factors, such as the duration of seizures, typically 30 min, or lack of return to baseline in between seizures [4, 5]. This definition is difficult to apply in neonates, as reliable electroencephalography (EEG) criteria are not readily available, and the majority of neonatal seizures are subclinical or subtle. Additionally, determining the neurologic baseline of an encephalopathic newborn often poses challenges.

Therefore, although neonatal seizures can be described with similar terminology as used for seizures in children and adults [4], neonatal SE may require an additional definition. Consequently, several studies refer to a measurement of an absolute seizure burden during a recording [2, 6, 7]. Seizure burden has been defined as the percentage of an epoch, typically an hour, during which there is electrographic seizure activity [6, 8]. This definition, however, does not correlate well with the assessment of seizures per hour (frequency) or of total seizure duration (summing the length of seizures over a particular epoch). To resolve this, calculating an "ictal fraction" by summing the overall duration of seizures in a period of time divided by the total recording time may provide a better picture of the individual seizure burden [9, 10]. The ictal fraction, however, will decrease with longer recording time, so neonatal SE should be defined as either an ongoing seizure for 30 min or total seizure time of 50% of an hour's recording [11, 12].

Epidemiology

Given the challenges of defining neonatal SE, it is, by extension, also difficult to assess incidence and prevalence. It is estimated that neonatal seizures occur in 1–5 out of 1000 live births, and in up to 5% of low birth weight infants [13–16]. The most common etiologies include hypoxic-ischemic injury, stroke, infections, and inherited structural causes [3, 14, 15, 17]. Less common but important causes of seizures and SE are metabolic conditions, such as hypoglycemia or inborn errors of metabolism [18, 19]. Finally, the highest proportion of patients with SE is likely to be those with neonatal epileptic encephalopathies, the most well-recognized being early

R.M. Guerriero · T. Loddenkemper (✉)
Neurology, Division of Pediatric and Developmental Neurology, Washington University School of Medicine and St. Louis Children's Hospital, 660 South Euclid Ave, Campus Box 8111, St. Louis, MO 63110, USA
e-mail: r.guerriero@wustl.edu

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infantile epileptic encephalopathy (EIEE, or Ohtahara's syndrome) and early myoclonic epilepsy (EME) [20].

Developmental Susceptibility

The relatively high incidence of seizures in the neonatal period may be related to an inherent predisposition to generating seizures. Normal neurobiologic processes of synaptogenesis and brain development that occur in the perinatal period require strong glutamatergic signaling. Additionally, there is also a propensity for gamma-aminobutyric acid (GABA)-mediated inhibitory circuitry to have a net excitatory effect on the developing brain in utero through at least the final trimester, thereby increasing the neonatal brain's susceptibility to seizures [21, 22].

In a fully developed brain, neuronal stress or injury leads to rapid depolarization of the presynaptic cell membrane, an influx of calcium ions, and release of the excitatory neurotransmitter glutamate. Glutamate then crosses the synapse to act on its receptors, specifically the *N*-methyl-*D*-aspartate (NMDA) and alpha-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptors. In the neonatal period, there is a greater number of these receptors due to the importance of glutamate in normal neuronal maturation [23].

Both the NMDA and AMPA receptors bear developmental signatures that lead to an imbalance of excitation and inhibition. Neonatal NMDA receptors are even more excitable than in the older brain, which is crucial for the development of the hippocampus and neocortex. In the neonate, NMDA receptors have increased glutamate binding and glycine activation—necessary for channel activation by glutamate. Additionally, there are changes in the inhibitory modulation of the NMDA receptor that leave it with a higher propensity for activation [12, 24, 25]. There are also changes in subunit expression, specifically over-expression of the NR2B subunit of the NMDA receptor [26–28]. The NR2B-containing neurons are uniquely positioned to cause cell injury and subsequent excitation based on their association with prolonged calcium influx [29–31]. Similarly, changes in the AMPA receptor lead to increased excitation [32]. In mature neurons, the GluR2 subunit decreases calcium permeability, thereby decreasing excitotoxicity. This subunit is decreased in the immature brain, and is further decreased by hypoxic-ischemic injury [33–35].

In addition to differences in the physiology of excitatory synapses in the immature brain, there is lower GABA-mediated inhibitory tone through the third trimester, further increasing the propensity toward excitation. The expression of GABA receptors is decreased in the developing brain [36, 37], and its inherent properties, including receptor subunit expression and the direction of the chloride ion (Cl^-) gradient, are different from that in mature neurons [38]. In the immature brain there is a relative over-expression of the α4 and α2 GABA subunits compared that of the α1 subunit [36, 37]. This pattern of subunit expression leads to resistance to benzodiazepines [36, 37] and has been shown to occur independently in SE [23, 36, 39]. Changes in subunit expression that predispose to seizures occur independently in both the immature brain and in SE and may thus be additive in the neonatal brain.

Furthermore, there are physiologic differences in the movement of Cl^- across the postsynaptic cell membrane. In mature neurons, GABA and its agonists bind to the postsynaptic receptors and promote Cl^- entry into the cell, thereby causing hyperpolarization and decreased cell firing. The opposite occurs in immature neurons, due to changes in the proteins that assist with ion transport across membranes. There is an over-expression in the sodium–potassium–chloride cotransporter 1 (NKCC1) and an under-expression of the potassium–chloride2 (KCC2) channel. NKCC1 pumps chloride ions into the cell, while KCC2 ion channels allow chloride to exit the neuron. Therefore, binding by GABA or other agonists to the GABA-A receptor on the postsynaptic cell prompts chloride ions to travel out of the cell, leading to membrane depolarization and increased excitation [40–42]. This difference between the developing and mature brain is currently under further investigation in clinical trials with bumetanide, an NKCC1 transporter inhibitor. Bumetanide blocks NKCC1, driving up the extracellular chloride ion concentration. Therefore, as GABA or a GABA agonist binds to the GABA-A receptor, chloride travels into and depolarizes the cell, and blocks epileptiform activity in hippocampal slices and seizures in neonatal rats [40].

Finally, this chloride gradient in GABA-A containing neurons matures in a caudal to rostral direction [43]. This maturation pattern may provide a neurophysiologic mechanism whereby electroclinical dissociation occurs, in which the clinical manifestation of seizures subsides with GABA agonist treatment, but the electrographic seizure persists. Subcortical GABA neurons may remain inhibitory during this period, leading to inhibition of subcortical motor innervation, while causing paradoxical excitation of cortical circuits [40].

Etiologies

The most common causes of status in a newborn are acquired neonatal brain injuries, including hypoxic-ischemic encephalopathy (HIE), infarction, and hemorrhage (Table 26.1) [14, 44]. Hypoxic-ischemic injury, typically caused by perinatal asphyxia, is the cause of seizures in 60–80% of infants [14, 38, 45]. When seizures occur in the setting of HIE, they often present within the first 12–24 h of

Table 26.1 Common etiologies of neonatal seizures, their relative frequency, and the prognosis for normal development in these conditions when they occur with seizures

Etiology	Timing of seizure (hours of life)	Frequency (%)	Normal development (%)
Hypoxic-ischemic encephalopathy (HIE)	0–24	60	50
Cerebral infarction	12–72	15	[a]
Intracranial hemorrhage – Term – Preterm	24–48 >72	15 45	10
Infection	>72	5–10	50
Genetic/structural	Variable	15	0
Hypoglycemia	0–48	3	50
Hypocalcemia	24–48	Rare	50–100

Modified from Volpe [14], with permission
[a]Developmental outcome is dependent on the severity and magnitude of cerebral infarction, as well as the presence of seizures [44]

life; most will be subtle seizures in the first 12 h, including SE [14]. Decreased oxygen delivery or blood flow, or both, lead to cell injury, placing these regions at risk for seizures. Additionally, the sodium–potassium–chloride cotransporter 1 (NKCC1), discussed above, is up-regulated in hypoxic-ischemic injury, providing another mechanism for seizure propensity in this population [46].

Focal cerebral infarction, or stroke, accounts for about 15% of seizures in neonates. In these patients, seizures often occur in the first 12–72 h of life [47, 48]. In contrast to encephalopathic infants with HIE, patients with focal stroke are otherwise well-appearing, without signs of encephalopathy.

Intracranial hemorrhages, including subarachnoid (SAH) and subdural hemorrhage (SDH), are less common causes of seizures and SE, but intraventricular hemorrhage (IVH) can be seen in up to 45% of preterm infants with seizures [47]. SAH is extremely common in term newborns and rarely causes seizures, but when it occurs it is usually at 24–48 h of life [49]. SDH is also a rare cause of seizures due to trauma. These are typically focal seizures occurring in the first 48 h of life [50].

Intracranial infection accounts for 5–10% of cases of neonatal seizures [14]. Common bacterial pathogens include Group B streptococci and *E. Coli*, with seizures usually occurring after day 5 of life [14, 51]. The most common nonbacterial pathogens include TORCH infections: Toxoplasmosis, Rubella, Cytomegalovirus (CMV), and Herpes simplex virus (HSV).

Another important cause of neonatal seizures and potentially, SE, is transient metabolic abnormalities. They may occur in isolation or more frequently, accompany other diseases. The three leading causes of these metabolic derangements are hypoglycemia, hypocalcemia, and hypomagnesemia. Hypoglycemia is the most common of these metabolic derangements, typically occurring in infants of mothers with gestational diabetes. These infants are small-for-age and, depending on the duration of in utero hypoglycemia, may have a variety of neurologic symptoms, including decreased mental status, apnea, and jitteriness, with seizures occurring in approximately 50% of patients, often around the second day of life [14, 52]. As with many of these conditions, hypo- or hyperglycemia may contribute to poor outcomes in the setting of underlying brain pathology, such as hypoxic-ischemic injury [53].

Hypocalcemia occurs more frequently in low birth weight infants in the first 2–3 days of life, but it may also be seen in normal-weight infants in the first 24 h. Calcium ions play a critical role in neuronal firing, in both pre- and postsynaptic cells. Most commonly, hypocalcemia occurs due to other conditions, including hypoglycemia or HIE [54, 55]. Similarly, hypomagnesemia occurs frequently in the setting of hypocalcemia but may occur independently. Hypomagnesemia produces a characteristic syndrome of hyperreflexia, jitteriness, and seizures [54, 56].

Less common causes of seizures in the newborn period include anesthetic intoxication due to local anesthetic administration during labor, and hyper- or hyponatremia related to a structural etiology, at times presenting with the syndrome of inappropriate antidiuretic hormone (SIADH), or due to iatrogenic hypernatremia [14].

Beyond transient metabolic abnormalities, inborn errors of metabolism and genetic and structural abnormalities may also lead to neonatal SE. These are frequently accompanied by neonatal epileptic encephalopathies. The two most well-recognized phenotypes are early myoclonic encephalopathy (EME) and early infantile epileptic encephalopathy (EIEE) or Ohtahara syndrome. These two syndromes, often caused by underlying genetic or metabolic conditions, are characterized by frequent clonic, myoclonic, and tonic seizures. The EEG is characterized by a "suppression–burst" pattern, where the suppression is more prominent than the bursts (Fig. 26.1). This

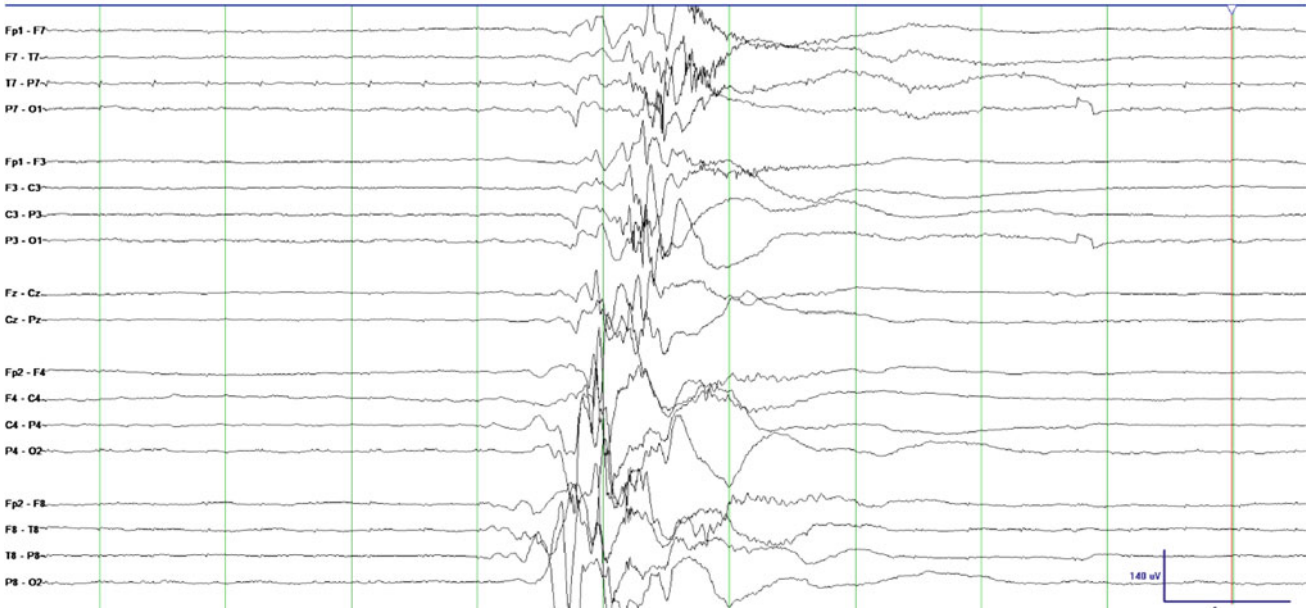

Fig. 26.1 Suppression–burst pattern of a neonatal epileptic encephalopathy. This patient had a clinical presentation and EEG on the spectrum between early myoclonic epilepsy (EME) and early infantile epileptic encephalopathy (EIEE) and was found to have a pyridox(am)ine oxidase (PNPO) mutation

pattern worsens during sleep in EME but is unchanged in EIEE. The suppression–burst pattern often persists in EME but typically transitions to hypsarrhythmia in EIEE [57, 58]. The phenotypes of these two syndromes are relatively similar. Traditionally, the etiologies have been considered diverse, with metabolic causes leading to EME and structural causes to EIEE. As more metabolic and genetic abnormalities become recognized, however, the phenotype–genotype correlation is becoming less clear, and these two syndromes may exist on a spectrum, rather than as isolated diseases.

One of the best characterized causes of neonatal epileptic encephalopathy is non-ketotic hyperglycinemia or glycine encephalopathy. This condition is due to an underlying defect of the glycine cleavage system, an enzyme complex consisting of four separate proteins. Defects in one of these proteins, most commonly the P- or T-proteins, lead to accumulation of glycine in the central nervous system (CNS). Excess glycine acts as both an excitatory and inhibitory transmitter in the CNS. It acts as an excitatory transmitter via NMDA receptors, leading to excess calcium entry into the cell and subsequent neuronal injury. The inhibitory glycine receptors are located in the brainstem and spinal cord and may contribute to the constellation of apnea, hypotonia, and in utero hiccupping that occurs in this condition. When glycine encephalopathy presents in the newborn period it is severe, with refractory myoclonic seizures, hypotonia, apnea, and encephalopathy [59]. Outcomes are poor, with a high mortality rate in the newborn period and profound neurodevelopmental delays in survivors. Treatments with sodium benzoate, which binds excess glycine, and with dextromethorphan to block NMDA receptors have been tried as treatments, with some improvement in outcomes [60].

Another inborn error of metabolism that is important to recognize given its distinct treatment is the spectrum of pyridoxine and pyridoxal-5-phosphate (P5P or PLP)-dependent epilepsy. Pyridoxine (or vitamin B6)-dependent epilepsy may cause SE in the newborn period. There are two known causes of pyridoxine-related epilepsy. The first, more common, type is related to a defect in antiquitin, an enzyme in the lysine degradation pathway that leads to build up of a toxic metabolite, alpha-aminoadipic-semialdehyde (AASA). AASA sequesters P5P, pyridoxine's metabolically active form, thereby limiting its availability as a cofactor in numerous reactions, including the synthesis of the inhibitory neurotransmitter GABA [61, 62].

The second, more recently discovered, pyridoxine-related epilepsy is due to a deficit in the enzyme pyridox(am)ine oxidase (PNPO) that converts pyridoxine to the metabolically active P5P. Defects in the quantity and functional configuration of PNPO have been identified in patients with early epileptic encephalopathies [63–65].

Another overlapping, rare but treatable cause of neonatal seizures is folinic acid-responsive epilepsy. This condition may present within the first several hours of life and responds to oral treatment with folinic acid [66]. Folinic-responsive seizures may be identical to pyridoxine-dependent seizures, given similar metabolites found on high pressure liquid

chromatography [67]. Of note, though, case reports of other conditions, including cerebral folate deficiency and STXBP1 mutation, are also responsive to folinic acid, implying that the field is still evolving [68, 69].

Disorders of glucose transport 1 (Glut1), encoded by the gene SLC2A1 (Solute Carrier Family 2 Member 1) are also becoming recognized as causes of seizures at all ages of childhood. Nearly 70% of patients present before 6 months of age and a quarter of these in the first 2 months of life. This condition is characterized by a low CSF glucose concentration compared with serum levels [70, 71]. The most effective treatment is the ketogenic diet [72]. See Table 26.2 [18, 73] for a summary of inborn errors of metabolism.

Finally, inherited structural etiologies may be the cause of neonatal seizures in 3–17% of patients [74]. These seizures and SE episodes may be refractory and include etiologies such as hemimegalencephaly, focal cortical dysplasia, pachygyria, polymicrogyria, and lissencephaly. Many of these structural causes of epileptic encephalopathies have been linked to genetic mutations [75]. Of particular interest, a link to the mammalian target of rapamycin (mTOR) pathway, which is involved in cell size and proliferation, has

Table 26.2 Summary of selected neonatal inherited metabolic epilepsies, with applicable lab tests, genetic defects, and treatment [18, 73]

Inherited metabolic epilepsies	Lab tests	Gene(s) involved	Treatment
Amino acidurias	Amino acids (serum)	Varied	Amino acid dependent
Organic acidurias	Organic acids (urine)	Varied	Organic acid dependent
Fatty acid oxidation defects	Lactate, pyruvate	Varied	Symptomatic
Mitochondrial disorders	Lactate, pyruvate, serum amino acids, urine organic acids, acylcarnitines	Varied	Cofactors and supplements
Urea cycle defects	Ammonia, acylcarnitines	Varied	Ammonia scavengers
Biotinidase deficiency	Ammonia, biotinidase activity	BTD	Biotin
Cerebral folate deficiency	CSF methyltetrahydrofolate	Folate receptor protein 1 (FR1)	Folinic acid
Disorders of creatine synthesis	Urine guanidinoacetate and MRS	GAMT, GATM, and SLC6A8	Disorder dependent
Glucose transporter deficiency (Glut1)	CSF: serum glucose ratio	SLC2A1	Ketogenic diet
Glycine encephalopathy	Glycine (serum and CSF)	Glycine cleavage proteins	Sodium benzoate, dextromethorphan
Menkes disease	Serum copper and ceruloplasmin	ATP7A	Copper injections
Molybdenum cofactor deficiency/sulfite oxidase deficiency	Urine sulfites and S-sulfocysteine	MOCS1 or 2, SUOX	Symptomatic
Pyridoxine-dependent epilepsy	AASA, pipecolic acid (serum)	ALDH7A1	Pyridoxine
PLP-dependent epilepsy	CSF PLP	PNPO	PLP
Pyruvate dehydrogenase deficiency	Lactate, pyruvate	PDH	Ketogenic diet
Serine deficiency (PHGDH deficiency)	CSF amino acids	PHGDH	L-serine
Succinic semialdehyde dehydrogenase deficiency (SSADH)	4-hydroxybutyric acid (urine, serum, CSF)	ALDH5A1	Symptomatic
Zellweger syndrome	Peroxisomal enzyme or very long chain fatty acid panel	PEX genes	Symptomatic

Abbreviations: *CSF* (cerebrospinal fluid), *AASA* (alpha-aminoadipic semialdehyde), *PLP* (pyridoxyl-5-phosphate), *PNPO* (pyridox(am)ine oxidase), *PHGDH* (3-phosphoglycerate dehydrogenase)

received increasing interest as a target of therapeutic interventions [76–78].

Clinical Semiology

Neonatal seizures tend to be focal, as opposed to generalized, and often have very subtle clinical findings [14, 79]. Classically, neonatal seizures have been identified based on clinical characteristics and criteria. Mizrahi and Kellaway, however, highlighted the notion that many of these movements and behaviors labeled as seizures did not have an EEG correlate [80]. Their study classified 425 clinical seizures in 71 infants and found that focal clonic, multifocal clonic, hemiclonic, and particular myoclonic and tonic seizures had a one-to-one correlation with epileptiform discharges on EEG, while more subtle oral-buccal movements, tremor, generalized tonic seizures, and other particular myoclonic seizures did not have a consistent EEG correlate [80].

Neonatal seizures and SE also have a high prevalence of subtle and electrographic-only seizures [47, 79, 81, 82]. Electrographic seizures occur in up to 90% of neonates who have seizures identified on clinically ordered video-EEG monitoring. Of those 90% with seizures, 12–79% have electrographic-only, or subclinical, seizures [1, 47, 83]. This high prevalence of electrographic-only seizures in neonates indicates that a large proportion of seizures may present without clinically recognizable signs.

Neonatal seizures can therefore be classified as subtle, clonic, tonic, or myoclonic [14], plus subclinical (or electrographic-only) seizures. Subtle seizures consist of a number of behaviors, movements, or phenomena that are not deemed clearly clonic, tonic, or myoclonic. For example, oral automatisms, eye deviation or fixation, and autonomic changes or apnea are all considered subtle seizures [14]. These subtle seizures may account for up to 68% of all preterm and up to 75% of term neonatal seizures [47]. Apnea is rarely a seizure on its own but may occur in conjunction with other subtle clinical phenomena [84, 85].

Clonic seizures consist of rhythmic, typically focal jerking of the face or extremities. These seizures are slower than in older children and adults. They may be focal or less commonly, multifocal. Focal, hemiclonic seizures are typically due to a cerebral infarction or similar focal lesion. Multifocal seizures often have a migratory pattern and should raise the suspicion for an underlying genetic or metabolic condition, such as malignant migrating partial epilepsy [86]. Tonic seizures may be focal or generalized, consisting of stiff, tonic posturing of an extremity or the neck, or bilateral extension of either upper or lower extremities. This type of posturing is most commonly non-epileptic, but when it is an electroclinical seizure it may be accompanied by autonomic symptoms [14]. Furthermore, myoclonic seizures are clinically faster and shorter than clonic seizures and more frequently involve flexor muscle groups [87]; they may be focal or generalized. Focal and multifocal myoclonuses are most frequently non-epileptic and without an EEG correlate. Conversely, generalized myoclonus has an EEG correlate about 60% of the time [80]. Myoclonic seizures are a common feature of neonatal epileptic encephalopathies, often with poor outcomes. Finally, generalized seizures are rarely seen in newborns, while a focal seizure that spreads to the contralateral hemisphere is associated with poor outcomes [9, 88, 89] (Fig. 26.2).

Neonatal seizures are typically brief, lasting 10 seconds to 2 minutes (min) but in severe cases may recur frequently, with a median interictal duration of 8 min [1]. To what extent there is return to baseline in between these seizures is often difficult to assess, particularly in an encephalopathic infant.

Diagnosis

In general clinical practice, patients are often treated based on the clinical seizure presentation. The limitations of this approach are magnified in the neonatal population where high numbers of seizures have either subtle or subclinical features. This may include up to 90% of patients with HIE who have no visible clinical correlates of seizures [90]. When infants have subtle seizures, the majority, about 70%, tends to present with eye movements [91]. Rarely, other subtle features, such as apnea and autonomic signs, are the only sign of seizures [85]. This highlights the crucial role of continuous video-EEG monitoring in the diagnosis of neonatal seizures and SE [7] (Fig. 26.3).

There are three additional features of neonatal seizure presentation that present a diagnostic challenge to the clinician. The first is uncoupling of the clinical and electrographic picture. This phenomenon, also known as electroclinical dissociation, occurs in very immature infants and often follows the administration of GABA-mediated medications [14, 47, 83]. As discussed earlier, GABA-mediated inhibition of the clinical motor manifestations acts through inhibitory subcortical receptors, while electrographic seizures persist due to the paradoxical excitation of cortical GABA receptors [14, 83].

This gives rise to the second problem in distinguishing between seizures and interictal phenomena seen frequently in ICU-EEG monitoring [92]. Key to the diagnosis of an ‘ictal’ discharge (i.e., sign of an ongoing seizure) in any setting, but particularly in neonates, is evolution of the electrographic pattern. An amplitude of at least 2 microvolts from peak-to-peak of the seizure waveforms and a duration of at least 10 seconds are often used as standards in the identification of electrographic seizures [1, 2, 6]. For example, brief rhythmic discharges (BRDs) and other periodic patterns often do not evolve and are therefore not

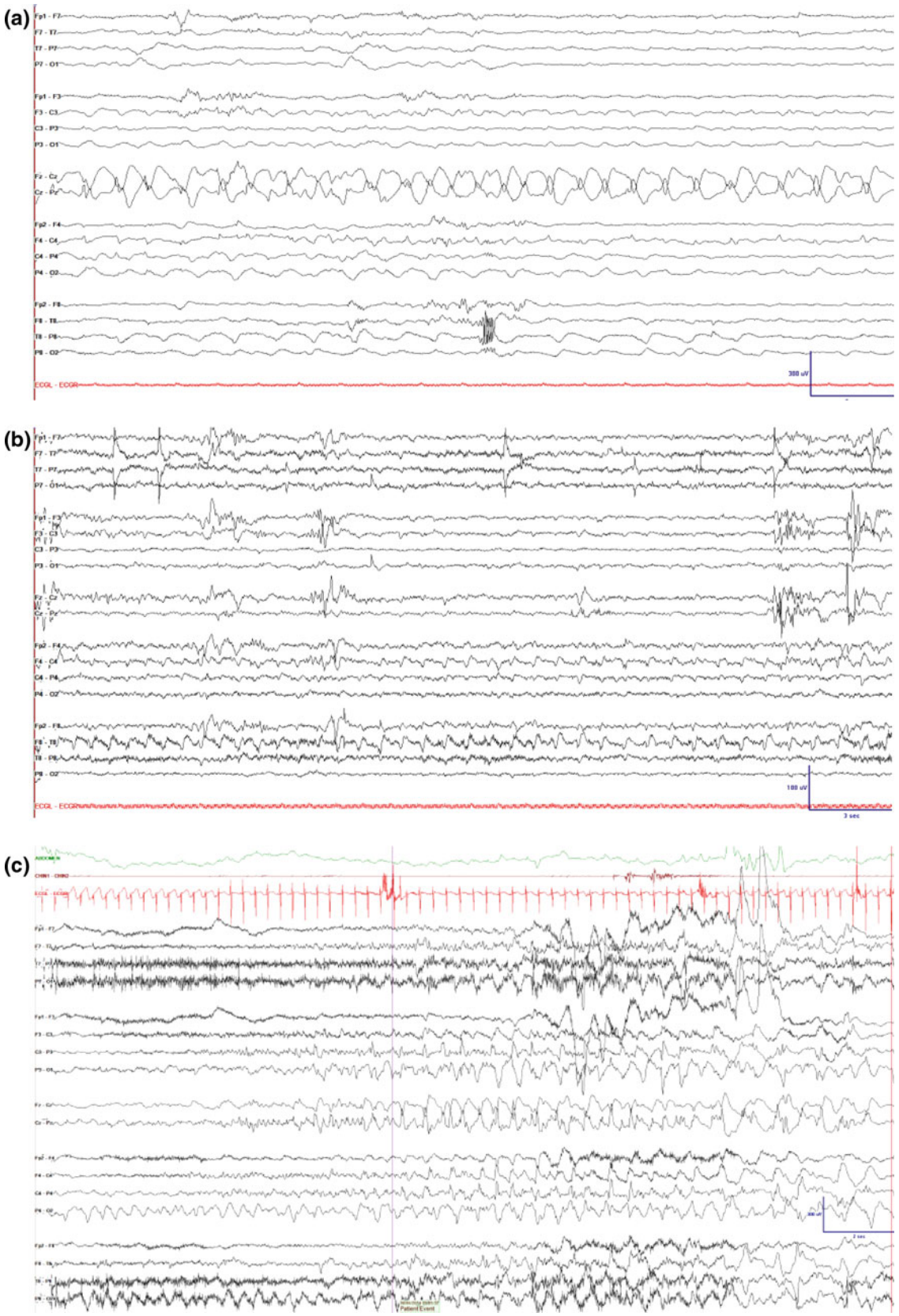

Fig. 26.2 Neonatal seizures. These EEGs show a range of neonatal seizures, ranging from single channel evolution in the central (**a**) or temporal (**b**) regions to those with more spatial evolution (**c**)

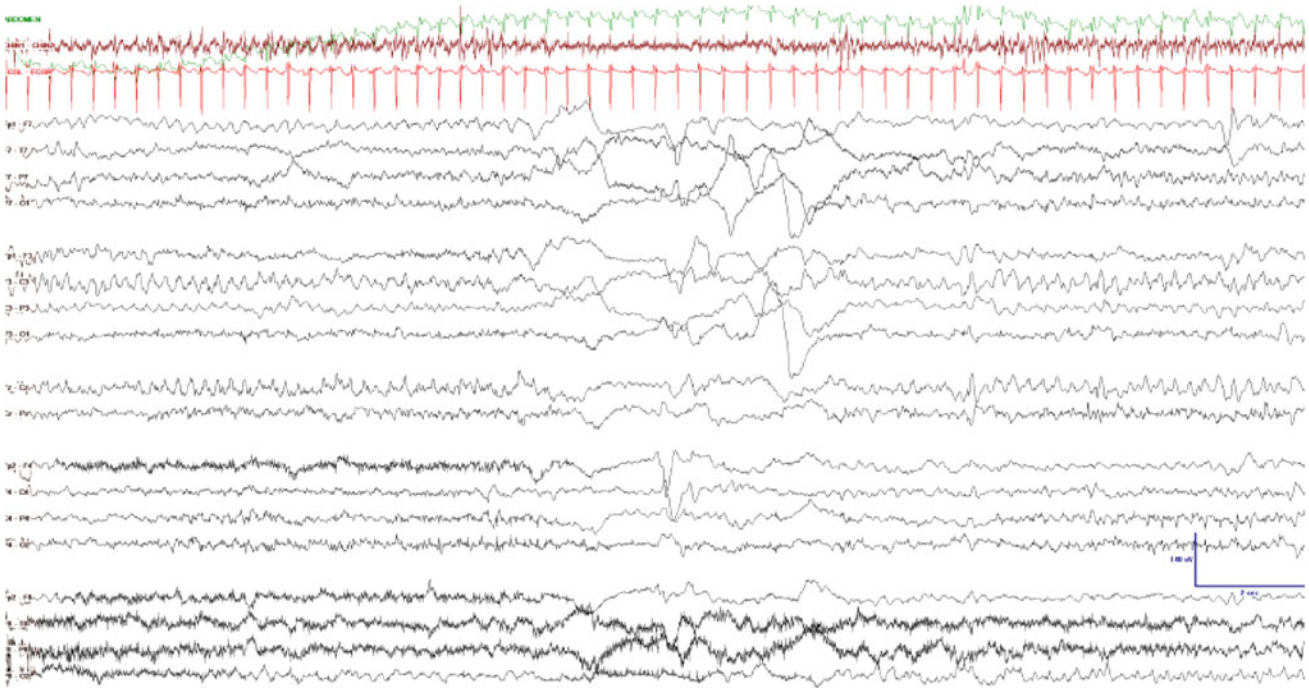

Fig. 26.3 Common neonatal artifact. This figure illustrates patting artifact and highlights how critical video-EEG is to distinguish this pattern from those in Fig. 26.2a, b

considered "ictal," and their implications for prognosis and clinical significance remain unclear. Additionally, Oliveira and colleagues showed that these BRDs are seen more frequently in neonates who have seizures than in controls, and are hence often associated with abnormal developmental outcome [93]. This highlights the complexity of the ictal–interictal continuum and implies that more research is needed to identify whether BRDs are simply an additional marker of an abnormal brain or an independent driver of neurologic compromise.

Finally, newborns also have a number of movements that are not associated with EEG changes, such as benign sleep myoclonus, jitteriness, and Bell's phenomenon, among others. Malone and colleagues assessed such clinical signs of seizures and non-seizures and found that trained neonatologists and nurses could identify only half of the actual electroclinical seizures based on clinical observation [94].

Treatment

Treatment of neonatal SE should target the resolution of both clinical and electrographic seizures. Treatment begins with phenobarbital, which is the standard of care until an alternative can be identified. A randomized trial of phenobarbital versus phenytoin indicated that phenobarbital led to an 80% reduction in seizures in 43% of patients; when phenytoin was added, this approached an 80% responder rate [95]. Dosing of phenobarbital is typically 20 milligram per kilogram (mg/kg) IV load, with subsequent boluses of 5 mg/kg up to an additional 20 mg/kg. Traditionally, phenytoin has been a second-line treatment, but its side effect risk has led to an increased use of levetiracetam at some centers [96, 97]. Fosphenytoin has overtaken phenytoin in common practice, but levels remain difficult to control in infants [98]. After phenobarbital and fosphenytoin, the use of a benzodiazepine such as lorazepam, diazepam, or midazolam should be considered [99, 100] (Table 26.3) [14, 73, 97, 101].

Through the course of treatment, it remains important to identify correctable causes of refractory seizures and SE, including transient causes, such as hypoglycemia and hypocalcemia, and inherited ones including pyridoxine-, P5P-, and folinic acid-responsive seizures, among others.

The relative ineffectiveness of standard SE treatments in neonates has prompted the investigation of supplementary and complementary therapies. One such potential treatment currently under investigation in clinical trials is bumetanide, which inhibits the NKCC1, thereby reversing the chloride gradient on postsynaptic cells, making GABA-A agonists more effective [102, 103]. In an open-label feasibility and safety trial, however, bumetanide did not improve seizure control and may have increased the risk of hearing loss in treated infants with hypoxic-ischemic encephalopathy [104]. Another trial of bumetanide is ongoing. Controlled trials of abortive medications are needed, but these studies are challenging given the existence of a current standard of care,

Table 26.3 Anti-seizure medication treatment of neonatal seizures [14, 73, 97, 101]

Medication	Bolus	Maintenance
Anti-seizure medications		
Phenobarbital	20 mg/kg, IV; additional 5 mg/kg up to a total of 40 mg/kg	5 mg/kg/day divided once or twice daily
Levetiracetam	40 mg/kg, IV; additional 20 mg/kg up to 60 mg/kg	40 mg/kg/day divided twice daily
Fosphenytoin	20 PE/kg, IV; additional 10 PE/kg	5 mg/kg/day divided every 8 h
Lorazepam	0.05–0.1 mg/kg, IV	
Midazolam	0.15 mg/kg, IV	Drip: 0.1–0.4 mg/kg/hr, IV
For selected treatable causes of epileptic encephalopathies		
Pyridoxine	100–500 mg IV with EEG monitoring	
Pyridoxyl-5-phosphate	30 mg/kg/day divided tid–qid × 3–5 days	
Folinic acid	3–5 mg/kg/day for 3–5 days	

Abbreviations: PE (phenytoin equivalents)

i.e., phenobarbital, despite that drug's adverse developmental effects [105, 106].

Prognosis and Outcome

The prognosis following neonatal seizures has improved over the last 50 years, with improved systemic and neuro-monitoring and management of infants in the neonatal intensive care unit. The underlying etiologies of neonatal seizures are the primary determinants of developmental outcome. There remains debate about the impact of seizures themselves on the developing brain. Comorbidities associated with prolonged seizures, including hypertension, apnea, and autonomic changes, have important systemic implications. As discussed, the immature brain appears more likely to generate seizures, but the neurons in infants may be at lower risk of cell death as compared to those in older children and adults [21, 24].

Nevertheless, animal and human data support the independent effect of seizures on developmental outcome. Animal data have shown that seizures exacerbate tissue injury, particularly in infants with hypoxic-ischemic injury [107]. These data hold up in a human study examining patients 4 years after HIE in whom the severity of seizures was an independent predictor of poor developmental outcome [108]. SE appears to be an independent contributor to poor outcome. In a study by Orbitus and colleagues, 27% of the 81 neonates observed had SE, and 86% of those with SE had a poor developmental outcome or death [109]. In another study of electrographic seizures (the distinction between clinical and subclinical was not made), infants with SE were more likely than those with seizures (but without SE) to have severe cerebral palsy and microcephaly, and they had a higher mortality [110].

Studying the outcome of neonatal status is complicated by the absence of a clear definition. Assessing seizure burden is likely the most important factor. Shellhaas and Clancy detailed the seizure frequency in 125 infants with an average of 7 per hour or an ictal fraction approximating 25% of the recording; a high seizure burden (greater than 50%) was considered SE [6]. A similar approach using seizure burden has been used for assessing electrographic seizures in critically ill older children, and this study also demonstrated implications for outcomes in this older population [8]. Although similar data in neonates are lacking, extrapolation of these data would support acceptance of the definition of 50% of a given hour defining a high seizure burden. Defining the number of seizures per epoch or the percentage of ictal burden may be even more important than the presence of prolonged seizures, as earlier studies suggest that more numerous shorter and recurrent seizures may have a worse prognosis than do more prolonged seizures [111, 112].

Finally, the relation between outcomes of preterm versus term infants has been studied recently by Pavlidis and colleagues who found a higher mortality rate in preterm infants [113]. This aligns with other studies suggesting that poorer outcomes are more often seen in premature and low birth weight infants [14].

Conclusion

Neonatal status epilepticus is a common but challenging diagnosis. Further clinical and basic research is needed to identify more effective therapies for prolonged neonatal

seizures, and additional work is needed to assess the degree to which seizure burden impacts outcome.

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Pediatric Status Epilepticus: Initial Management and the Special Syndromes of Status Epilepticus in Children

27

James J. Riviello

Introduction

Status epilepticus (SE) is a life-threatening medical emergency that requires prompt recognition and emergency treatment to reduce morbidity and mortality [1–4]. SE is not a specific disease in itself; it results from a primary central nervous system (CNS) insult, or a systemic disorder with secondary CNS effects. SE is defined by the actual seizure time, and its semiology is divided into convulsive SE and nonconvulsive SE (NCSE). Treating the precipitating cause is important for control, with symptomatic SE more common in younger children and infants. Evidence-based guidelines for the diagnostic assessment of SE in children [5] and SE treatment guidelines exist [6, 7]. The evaluation and management of SE is similar in adults and children, but unique syndromes of NCSE occur in children [2], including the epileptic encephalopathies.

This chapter shall discuss the initial presentation and management of SE, acute repetitive seizures (ARS), and the unique syndromes of SE in children and review the new definition and classification of SE [8]. Neonatal SE and continuous electroencephalogram (EEG) monitoring in the pediatric intensive care unit (PICU) are discussed in other chapters.

Definition

The definition and classification of SE have been updated by the International League Against Epilepsy (ILAE) Task Force on Classification of SE to include four axes [8]. SE is now defined as "a condition resulting from either the failure of the mechanisms responsible for seizure termination or from the initiation of mechanisms which lead to abnormally prolonged seizures (after time point t1). It is a condition which can have long-term consequences (after time point t2), including neuronal death, neuronal injury, and alteration of neural networks, depending on the type and duration of seizures." The original ILAE definition of SE, by Gastaut: "an epileptic seizure that is sufficiently prolonged or repeated at sufficiently brief intervals so as to produce an unvarying and enduring epileptic condition" [9], although vague, has allowed a dynamic interpretation. Subsequently, SE was defined specifically as continuous seizure activity or recurrent seizures without recovery of consciousness for greater than 30 min [10]. SE was later defined 'operationally' (for treatment purposes) as greater than 5 min of either continuous seizure activity or recurrent seizures without recovery in between [11]. In the recently updated classification, the operational definition (i.e., duration criteria) now varies by seizure type: for tonic-clonic SE, t1 = 5 min, and t2 = 30 min; for focal SE with impaired awareness, t1 = 10 min and t2 > 60 min; for absence SE, t1 = 10–15 min, and t2 is unknown [8].

The four axes in the new classification [8] (Table 27.1) are Axis 1: semiology; Axis 2: etiology; Axis 3: EEG Correlates; and Axis 4: age [8]. Previously, the International Classification of Epileptic Seizures (ICES) was by seizure type, based on seizure onset location, whether partial (focal) or generalized [12], or modified by semiology [13], i.e., convulsive (generalized tonic clonic) SE, nonconvulsive SE (NCSE) (absence or complex partial), or simple partial (focal) SE. NCSE occurs with either generalized (absence) or focal (partial complex) epilepsy. Although NCSE typically has no outward signs, careful observation commonly detects some clinical manifestations [14].

The semiologic classification is now divided into SE with prominent motor symptoms and without prominent motor symptoms (NCSE) (see Table 27.1). The special syndromes of SE are now recognized in the new classification system as

J.J. Riviello (✉)
Professor of Pediatrics and Neurology, Associate Section Head for Epilepsy, Neurophysiology, and Neurocritical Care, Section of Pediatric Neurology and Developmental Neuroscience, Texas Children's Hospital, Baylor College of Medicine, 6701 Fannin Street, Suite 1250, Houston, TX 77030, USA
e-mail: riviello@bcm.edu

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Table 27.1 The 2015 International League Against Epilepsy Classification of Status Epilepticus (SE)

Axis 1: Semiology
(A) With prominent motor symptoms
A.1: Convulsive SE (CSE)
A.2: Myoclonic SE
A.3: Focal motor SE
A.4: Tonic SE
A.5: Hyperkinetic SE
(B) Without prominent motor symptoms [nonconvulsive SE (NCSE)]
B.1: NCSE with coma (including subtle SE)
B.2: NCSE without coma
Axis 2: Etiology
Known (symptomatic)
Acute
Remote
Progressive
SE in defined electroclinical syndromes
Unknown (cryptogenic)
Axis 3: Electroencephalogram (EEG) correlates
1. Location: generalized, lateralized, bilateral independent, multifocal
2. Name of pattern: periodic discharges, rhythmic delta activity, spike and waves or sharp and wave subtypes
3. Morphology: sharpness, number of phases, absolute and relative amplitude, polarity
4. Time-related features: prevalence, frequency, duration, daily pattern duration and index, onset, and dynamics (evolving, fluctuating, static)
5. Modulation: stimulus-induced versus spontaneous
6. Effect of intervention (medication) on EEG
Axis 4: Age
1. Neonatal (0–30 days)
2. Infancy (1 month–2 years)
3. Childhood (>2 to 12 years)
4. Adolescence and adulthood (>12 to 59 years)
5. Elderly (>60 years)

From Trinka et al. [8], with permission

"indeterminate conditions, or boundary syndromes" [8]. These include the epileptic encephalopathies and electrical status epilepticus of sleep (ESES).

Etiology is included in the classification [8], now as Axis 2: Known (or 'symptomatic') or unknown (or 'cryptogenic'). Symptomatic includes acute, remote, progressive, and SE in defined electroclinical syndromes (Table 27.2) and includes acute symptomatic, remote symptomatic, remote symptomatic with an acute precipitant, progressive encephalopathy, cryptogenic, idiopathic, and febrile SE [15]. Remote symptomatic SE has been called 'acute on chronic' [16]. Defined electroclinical syndromes are now included under etiology. The SE classification also includes pseudoseizures because pseudostatus epilepticus also occurs in children [17, 18].

By age, neonatal SE includes ages 0 through 30 days (see Table 27.1). Neonates (<1 month old) are typically excluded from SE series because neonatal seizures and EEG features differ from those of adults. The Richmond SE study compared neonatal EEGs to those of 1- to 6-month-old infants. Neonates generally have shorter seizures and several seizure foci, whereas infants over 2 months of age could generate prolonged seizures and generally had several foci, and secondary generalization could occur [19].

Stages of Status Epilepticus

Status epilepticus is divided into clinical stages: premonitory (prodromal); incipient (0–5 min); early stage (5–30 min); the transition stage, from the early to the late, or established, stage (30–60 min); refractory stage (greater than 60 min); and post-ictal stage [1, 20] (Table 27.3). The premonitory

Table 27.2 Etiologic classification of seizures and status epilepticus [5, 8, 15]

Acute symptomatic: associated with an acute CNS insult (e.g., stroke, intoxication, encephalitis)
Remote symptomatic: seizure disorder or epilepsy in the setting of a past CNS insult (e.g., post-traumatic, post-encephalitis, post-stroke)
Remote symptomatic with acute precipitant: an acute insult (precipitant) superimposed on a past CNS insult; also called acute on chronic
Progressive encephalopathy: associated with a progressive degenerative or metabolic disorder (e.g., brain tumor)
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, inflammation: meningitis, encephalitis, or inflammatory cause)
SE in a defined electroclinical syndrome (e.g., epileptic encephalopathy, Lennox–Gastaut syndrome, Landau–Kleffner syndrome)
Non-epileptic SE (i.e., pseudo SE)

CNS central nervous system, *SE* status epilepticus

stage consists of confusion, myoclonus, or increasing seizure frequency. The early stage has continuous seizure activity whereas convulsive SE (CSE) evolves into NCSE in the refractory stage. If a premonitory stage is identified, treatment should be initiated (see pre-hospital treatment). Specific circumstances may require immediate seizure control in the incipient stage (0–5 min). We have called these the special circumstances of the early stage (Table 27.4) [1, 4]. The t1 and t2 time points of the new system are analogous to the transition stage, which may vary under different circumstances. ARS should be considered a 'premonitory' stage of SE and may be SE if there is no return to baseline mental status in between seizures.

Treiman reported that the EEG stage of SE correlates with the clinical stage and may occur in a predictable sequence: (1) discrete seizures with interictal slowing; (2) waxing and waning of ictal discharges; (3) continuous ictal discharges; (4) continuous ictal discharges punctuated by flat periods; and 5) periodic epileptiform discharges (PED), on a flat background [21] (Table 27.5). Early anti-seizure drug (ASD) treatment controls seizure activity better than when administered in a later stage [21]. One case reported an adult who went through all of these EEG stages during continuous EEG (C-EEG) monitoring [22], but not every episode of SE passes through each stage [23]. The PED stage may also consist of either bilateral (BPED) or lateralized (PLED) patterns [24]. These same stages have been documented in the developing brain in experimental animals [25]. The new classification includes the EEG correlates of SE; these include the location, name of pattern, morphology, time-related features, modulation, and effect of intervention with medication (see Table 27.1).

SE treatment had been divided into first-line through fifth-line, with recommendations for certain medications to be administered in sequence based on times from seizure onset. The Neurocritical Care Society SE guideline recommends that treatment terminology be changed from that of first through fifth-line therapy to 'emergent' initial therapy, urgent control therapy, and refractory therapy [3]. Hopefully, this change will shift treatment mentality from that of focusing on timelines from seizure onset to that of achieving seizure control. Therefore, SE is now defined by the time from seizure onset (t1) and the response to ASD treatment: SE, established SE (failure to respond to emergent therapy), and refractory SE, defined as SE not responding to the initial benzodiazepine and the second-line ASD [8, 26].

Table 27.3 Clinical stages of status epilepticus and corresponding time from seizure onset (t1)

Clinical stages	**Minutes**
Premonitory	Before SE (t1)
Incipient	0–5
Early	5–30 (t2)
Special circumstances (see Table 27.4)	
Transition	May vary
Late (established)	30–60
Refractory	>60
Post-ictal	After SE
(Need to exclude NCSE if not returning to baseline)	

Adapted from [1, 2, 8, 20]

Table 27.4 Special circumstances, early stage of status epileptics [1, 2, 4]

Postoperative patients, especially after 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

CNS central nervous system

Table 27.5 Stages of status epilepticus according to Electroencephalogram (EEG)

Discrete seizures with interictal slowing
Merging seizures
Continuous ictal discharges
Continuous ictal discharges punctuated by flat periods
Periodic epileptiform discharges (PEDs)

From Treiman et al. [21], with permission

Epidemiology of Status Epilepticus

Status epilepticus is common in childhood-onset epilepsy. In a population-based study from Connecticut, 56 of 613 children (9.1%) had one or more episodes of SE [27]; from a Finnish cohort of children with epilepsy, 41 of 159 (27%) had SE. SE was more likely within the first 2 years after the onset of epilepsy; risk factors for SE included remote symptomatic cause, onset at age 6 years or younger, and partial seizures [28]. In a study of 394 children with SE from Richmond and the Bronx, SE was common in younger children, with over 40% of episodes occurring in those aged 2 years or less, and of these, over 80% had a febrile or acute symptomatic etiology; cryptogenic or remote symptomatic etiologies were most common in older children, as was a prior history of epilepsy [29]. In a prospective study, SE recurred in 16 of 95 cases (17%). Neurologic abnormalities (including severe cognitive or motor developmental delay or both, progressive encephalopathy, mental retardation, cerebral palsy, genetic syndromes, or multiple congenital anomalies) were found in 34% of all patients, but in 88% of those with two episodes of SE, and in all five patients with three or more episodes of SE [30]. 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.

Five population-based studies of SE include children [31–35]. The incidence varies from 41 cases per 100,000 people in Richmond [32], to 18/100,000 in Rochester [33], 10/100,000 in Switzerland [34], and 6.2/1,000,000 in California [35]. All studies show a higher incidence of SE in the youngest children and the elderly. The Richmond study stratified the incidence by age: 156/100,000 in infants, 38/100,000 in children, 27/100,000 in adults, and 86/100,000 in the elderly [32]. In the North London SE in Childhood Surveillance Study (NLSTEPSS), the age-adjusted incidence for acute symptomatic SE was 17/100,000 in children less than one year of age, 2.5/100,000 in those of age 1–4 years, and 0.9/100,000 in those 5–15 years of age. The incidence of an episode of acute on remote symptomatic SE (remote symptomatic with an acute precipitant) was 6, 5.3, and 0.7%, respectively, in the above age groups. A prolonged febrile seizure occurred in 4.1 cases per 100,000 population; acute symptomatic causes in 2.2/100,000; remote symptomatic in 2.3/100,000; acute on remote in 2.1/100,000; idiopathic in 1.4/100,000; cryptogenic in 0.2/100,000; and unclassified in 1/100,000 in children of all ages [16].

Etiology and Prognosis

The 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 on pediatric SE by Aicardi and Chevrie, including 239 children, 113 cases were symptomatic and 126 were cryptogenic [36]. In those with symptomatic SE, 63 of 113, or 26% overall, had acute CNS insults (including treatable disorders such as bacterial meningitis, encephalitis, dehydration or electrolyte disorders, toxic ingestions, or subdural hematoma), and 50, or 21% overall, had a remote symptomatic cause, also referred to as a chronic

encephalopathy (e.g., anoxia, progressive encephalopathy, non-progressive encephalopathy, brain malformation, cerebral palsy, and Sturge–Weber syndrome). In those with cryptogenic SE, 67 of 126 (or 28% overall) were associated with fever (a prolonged, or complex, febrile seizure). In another classic study, Maytal et al. [37] reported similar data for etiology: 45 of 193 patients (23%) had acute symptomatic and 45/193 (23%) remote symptomatic causes. In the NLSTEPSS prolonged febrile seizures occurred in 32% of all SE cases, acute symptomatic SE in 17% of all cases, remote symptomatic SE in 16% of all cases, and acute on chronic SE in 16% of all cases [16].

The incidence of SE of different etiologies differs in children and adults. The Richmond Study included all ages; the most common cause of SE in adults was cerebrovascular disease (25.2%) whereas fever or infection (35.7%) was the most common cause in children [38]. Recent medication changes occurred in 20% of children and 19% in adults (Table 27.6). Symptomatic SE has a greatest frequency in the very young and has a higher morbidity and mortality. It occurs less frequently after one year of age. Idiopathic SE (in children without an underlying neurologic abnormality) is rare during the first several months but becomes more common after 6 months [39].

The SE mortality in children ranges from 3 to 11% and also varies by etiology and age [36, 37, 40–46]. In the Maytal study, the overall mortality was 4%, with deaths occurring only in those with an acute symptomatic or progressive symptomatic etiology [37]. The lowest mortality, 3%, was from Saudi Arabia [46]. The Richmond study had an overall mortality of 6% [39]; when age-stratified, the first-year mortality was 17.8%, but in the first 6 months, mortality was 24% compared to 9% in those aged 6–12 months. This difference results from a higher incidence of symptomatic SE in the youngest children [39]. Regarding morbidity, a Canadian study showed that 34% of 40 children with a seizure duration of 30–720 min had subsequent developmental deterioration [47]. Some of the morbidity and mortality of SE may be a direct consequence of the SE itself and some attributed to the illnesses underlying the SE [48]. An increased morbidity and mortality also occurs with NCSE, especially with a duration greater than 36 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. Benign febrile seizures are typically short, <15 min, non-focal, and not associated with a prolonged post-ictal state [52]. Febrile SE (FSE) is a subgroup of febrile seizures. In the Richmond series, over 50% of SE in children occurred due to infection, versus only about 5% in adults [38]. The NLSTEPSS data are similar, with prolonged febrile seizures occurring in 32% of children with convulsive SE [15]. A symptomatic cause, especially meningitis or encephalitis, must be excluded. There is also controversy regarding the prognosis of FSE. An Italian study 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 [55] reported a better prognosis of FSE in the neurologically normal child. The British National Cohort Study also found that the prognosis for lengthy febrile seizures and SE was determined more by the cause [56].

In a cohort of 381 Japanese children with febrile SE, 81.6% had prolonged febrile seizures, 6.6% had encephalopathy or encephalitis or both, 0.8% had meningitis, and 7.6% had previously diagnosed epilepsy. The seizures were longer in the encephalopathy/encephalitis cases than in the prolonged febrile seizures [57], but an earlier British Study found four cases of bacterial meningitis in 49 cases of febrile SE [58].

Table 27.6 Comparison of etiologies in children and adults in the Richmond Study

Etiology	Children (<16 years) (% cases)	Adults (>16 years) (% cases)
Cerebrovascular	3.3	25.2
Medication change	19.8	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

From DeLorenzo et al. [38], with permission
CNS central nervous system

A prospective study to determine the consequences of FSE is in progress, the Consequences of Prolonged Febrile Seizures in Childhood (FEBSTAT) study. Patients are included for analysis if they have a seizure or series of seizures without full recovery lasting >30 min, fever >38.4 °C, with ages 1 month through 5 years, with no acute CNS insult or infection and no prior afebrile seizures [59]. So far, the data have been analyzed for cerebral spinal fluid (CSF), EEG, and neuroimaging. An LP (done in 154 of 200 cases) was non-traumatic in 136; 116 of 136 had <3 WBCs; the largest number was 12 in one child [60]. Acute EEG findings were analyzed in 199 children; 90 of 199 (45.2%) were abnormal, with non-epileptiform abnormalities in 85 (42.7%) and epileptiform abnormalities in 13 (6.5%) [61]. MRI findings showed hippocampal enlargement and increased signal in 11.5% and a malrotation of the hippocampus in 10.5% [62]. The long-term goal of FEBSTAT is to identify risk factors for mesial temporal (hippocampal) sclerosis, which may result from prolonged febrile seizures.

Diagnostic Evaluation

The treatment of a seizure, ARS, or SE starts with following the A, B, Cs (Table 27.7) and performing appropriate diagnostic studies (Table 27.8). Convulsive SE is relatively easy to recognize, but NCSE and nonconvulsive seizures require EEG identification. Appropriate diagnostic studies are determined by the history and examination. If the seizure occurs in the setting of an acute illness, especially with vomiting and diarrhea, hypoglycemia, electrolyte disturbances, and dehydration must be considered [1, 2, 4]. Even with a nonspecific upper respiratory tract infection, there may be an underlying disorder, with symptoms precipitated by the metabolic stress such as with a metabolic or mitochondrial disorder. Preceding psychiatric symptoms, movement disorders, or a family history of autoimmune disorders may be suggestive of an acute autoimmune disorder (e.g., NMDA receptor encephalitis). The patient must be stabilized before further testing, such as lumbar puncture or transport to neuroimaging.

Serum glucose should be checked rapidly by point-of-care testing to exclude hypoglycemia. A CBC may be helpful for suggesting infection, but leukocytosis may occur from the SE itself. Electrolytes, calcium, phosphorus, and magnesium values may be helpful in children with vomiting and diarrhea [63]. Low ASD levels may be associated with SE [64]. Serum studies may be needed if there is suspicion for a specific toxin [5].

The American Academy of Neurology (AAN) and the Child Neurology Society practice parameter on diagnostic abnormalities in SE found the following, when tested [5]: abnormal electrolytes (6%), positive blood cultures (2.5%), CNS infection (2.8%), low ASD levels (32%) ingestion of some toxic substance (3.6%), inborn errors of metabolism (4.2%), epileptiform abnormalities on EEG (43%), and neuroimaging abnormalities (8%). In a prospective study of new onset SE with an acute symptomatic etiology, febrile SE occurred in 32%, CNS infection in 9%, vascular causes in 3.4%, and electrolyte abnormalities, toxins, and trauma in 1.4% each [65]. With a remote symptomatic etiology, cerebral dysgenesis and inborn errors occurred in 5.6% each, 2.8% had a remote vascular cause, and a remote infection, chromosomal abnormality, or mesial temporal sclerosis occurred in 1.4% each.

In a review, Freilich et al. [66] recommended that electrolytes, EEG, and CT or MRI scans should always be done for new onset SE, and if the clinical suspicion exists, urine toxicology, genetic or metabolic testing, and lumbar puncture should also be considered. For refractory SE or with persistent encephalopathy, C-EEG monitoring is recommended. For SE in a known patient with epilepsy, ASD levels are always recommended, and electrolytes, EEG, and CT or MRI scan, and (if febrile) a lumbar puncture (LP), should be considered. With refractory or persistent encephalopathy, C-EEG monitoring [66] is recommended.

Meningitis can be a frequent cause of SE in children with fever, occurring in 4 of 24 cases in a prospective study [58]. Therefore, LP to exclude meningitis must be considered in every febrile child with a seizure or SE. The child may be assessed clinically if old enough, but the signs of meningitis may be absent in infants or after CSE [58]. If there is concern for increased intracranial pressure or a structural lesion, LP is deferred until neuroimaging is performed. In this situation, antibiotic treatment should be initiated prior to the LP, ultimately relying on the cell count and bacterial cultures to exclude an infection. CSF pleocytosis may occur without infection [67], due to either a CNS inflammatory process or breakdown in the blood–brain barrier from the seizure activity. The FEBSTAT, however, showed that CSF pleocytosis is unlikely in FSE, occurring in only 20 of 136 cases (15%) [60].

The AAN practice parameter for neuroimaging in seizures recommended an ‘emergent’ scan (immediately) for new onset SE or SE in a child with known epilepsy not responding to treatment [68, 69]. A greater incidence of life-threatening lesions (e.g., hemorrhage, brain swelling, mass effect) occurs with a first-time seizure or in a child with epilepsy and new focal deficits, persistent altered mental status, with or without intoxication, fever, recent trauma, persistent headache, cancer, or on anticoagulation [68–70]. MRI is more sensitive than CT scan but is rarely available for emergency studies; CT scans will identify life-threatening conditions adequately. In a study of new onset seizures presenting with SE, a diagnosis was made by neuroimaging (CT or MRI) in 30%, with management

Table 27.7 Initial management of the incipient stage of pediatric status epilepticus

What do to first: the **A**, **B**, **C**s
Stabilize and maintain the **A**irway (jaw lift)
Establish **B**reathing (i.e., ventilation)
Maintain the **C**irculation
Monitor vital signs: pulse, pulse oximetry, respiratory rate, blood pressure, temperature
Oxygen
Position head to prevent or relieve airway obstruction; jaw lift
Early intubation to protect airway, provide adequate oxygen, and ventilation
Establish IV access; blood testing:
Serum glucose (point-of-care testing)
CBC, differential
Chemistry: electrolytes, BUN, creatinine, Ca, Phos, Mg, glucose
ASD levels, if applicable
Toxicology studies (urine, serum), if applicable

IV intravenous; *CBC* complete blood count; *BUN* blood urea nitrogen, *Ca* calcium, *Mg* magnesium, *ASD* anti-seizure drug

Table 27.8 Other tests with in the diagnosis of pediatric status epilepticus

Lumbar puncture	To exclude meningitis, encephalitis, or subarachnoid hemorrhage. If there is concern for increased intracranial pressure (e.g., coma, focal neurologic examination, papilledema), LP should be deferred until cranial CT scan is done
Electroencephalogram	Needed initially only if there is unexplained altered awareness, to exclude nonconvulsive SE, or if the diagnosis is in doubt, especially for nonepileptic attacks, or when there has been no improvement in mental status within 30 min despite control of convulsive movements (also to exclude NCSE)
Neuroimaging	Emergency neuroimaging with CT scan needed with unexplained SE, especially if new onset, focal SE, or associated with focal neurologic signs, or if there is concern for increased intracranial pressure before LP. This is done after the patient has been 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

CT computed tomography, *SE* status epilepticus, *NCSE* nonconvulsive status epilepticus, *LP* lumbar puncture

changed in 28 of 143 cases (24%), and 20% of cranial CT scans were abnormal, with 14 (10%) showing acute abnormalities, and 14 (10%) showing chronic abnormalities [65]. In a study of 71 cranial CT scans in children with new onset seizures admitted to the PICU, abnormal findings occurred in 16 of 71 patients (22%); clinically significant findings occurred in 14 of these; and findings resulted in a change in management in 5 of 14 patients, representing 7% of the original group. The findings that led to change in management included subdural hematoma, mass with midline shift and hydrocephalus, and arteriovenous malformation with intracranial hemorrhage (in one child each) and communicating hydrocephalus in two children. Risk factors for a positive scan included lack of fever, multiple seizures, and age less than 24 months [71]. It is imperative to stabilize the child before transport to the neuroimaging suite.

An immediate EEG is not usually done during the initial treatment of CSE, unless there is a strong suspicion for non-epileptic events. If convulsive movements stop after the initial therapy, without an improvement in consciousness, however, an EEG is needed to exclude NCSE. In adults, NCSE occurred in 14% of patients treated for CGSE [72]. In children, NCSE occurred in 5 of 19 cases following control of CSE; in 2 of these, NCSE occurred after treatment of CSE and in 3, NCSE occurred after treatment of RSE [73]. After the control of outward seizures in 98 children with CSE, electrographic seizures were seen in 32 of 98 cases (33%), and NCSE was present in 15 of 98 (15%) [74]. In comatose patients of all ages without obvious seizure activity, NCSE was detected in 8% [75], and in a study of children only, NCSE was detected in 2 of 19 patient following an hypoxic-ischemic insult [73].

The other indications for emergency EEG include unexplained altered awareness (to exclude NCSE); neuromuscular paralysis for SE, which eliminates the convulsive movements by neuromuscular blockade but does not stop the

electrographic seizure activity; or when continuous intravenous (IV) therapy is needed for refractory SE (RSE) [76]. The EEG is useful whenever the diagnosis is in doubt, especially for non-epileptic events [77]. In one report, 6 of 29 children admitted with CSE had non-epileptic events [17].

Therapy for Status Epilepticus

As mentioned, treatment protocols have generally been time-based, with specific ASDs recommended after various times from seizure onset. At seizure onset, supportive measures must maintain the airway, breathing, and circulation (the A, B, Cs). The initial management of a seizure is detailed in Table 27.7. Vital signs are taken, oxygen is administered, IV access is secured, and initial blood studies sent. Many seizures will stop spontaneously while the above are in progress. If the seizure continues for 5 min, a first-line ASD is given. If the initial medication fails, then second-line treatment, followed by third-, fourth-, and fifth-line agents are used. These ASDs should be given in an IV formulation. Lorazepam has replaced diazepam (DZP) as first-line therapy [2]; these two agents have equal efficacy for controlling the seizure initially, but there is a shorter anticonvulsant duration with DZP, and repeat doses may be required [78, 79]. Midazolam is also used as a first-line agent. If lorazepam does not work within 5 min, many protocols repeat the dose and then administer the second ASD.

The initial benzodiazepine dose is given rapidly by an IV push. Subsequent IV ASDs are given by an IV loading dose. These have a fixed infusion time in order to prevent adverse effects, notably hypotension or cardiac arrhythmias. If the second agent does not work, the third agent is given, also with a specific infusion time. As it takes time to give a therapeutic dose, these infusion times can delay seizure control. Waiting for the infusion to be completed may increase the chance of brain injury, especially when the brain's compensatory mechanisms are compromised. If there is no IV access, midazolam, 0.2 mg, or fosphenytoin, 20 mg/kg, may be given IM. Alternatively, rectal diazepam may be administered.

Historically, phenobarbital, phenytoin, and the benzodiazepines, diazepam and lorazepam, have been the first-line agents. The Veterans Affairs Cooperative Study assessed drug efficacy in adults with SE, comparing lorazepam (0.1 mg/kg), phenobarbital (15 mg/kg), diazepam (0.15 mg/kg) plus phenytoin (18 mg/kg), and phenytoin alone (18 mg/kg). Successful treatment was defined as SE control within 20 min. Efficacy was similar with lorazepam (65%), phenobarbital (58%), and diazepam plus phenytoin (56%), whereas phenytoin alone had a lower rate (44%). This lower rate was likely related to the infusion time needed: 4.7 min with lorazepam versus 33 min with phenytoin alone [80]. IV preparations of valproate, levetiracetam, and lacosamide are now available.

In children, many use the following sequence after lorazepam: fosphenytoin, followed by phenobarbital, then midazolam—which is followed by pentobarbital if seizure activity continues, considered RSE [81]. The American Epilepsy Society evidence-based guideline for the administration of ASDs in SE is shown in Table 27.9 [26]. In the NLSTEPSS treatment study, seizures stopped after a first-line agent in 65% and after a second-line agent in only 50% of the remainder (41/82); when the initial benzodiazepine dose was repeated, it worked in only 1 of 16 cases [82]. From Izmir, only 2 of 27 cases were controlled by first-line therapy (diazepam), whereas midazolam controlled 22 of 23 cases when used at various stages, including 3 treated in the early stage [83]. A study from Athens used a repeat midazolam bolus of 0.1 mg/kg every 5 min in children with chronic epilepsy, with a maximum of 5 doses; this protocol controlled 53% after one dose, another 26.3% after a second dose, and another 10.5% after the third dose, with a total of 90.7% control after five doses [84]. In the NLSTEPSS, it was common for lower doses to be used [82]. Pediatric treatment protocols need to be updated, to stop the SE more aggressively when it is considered refractory SE (e.g., after failure of the initial BZP followed by the second-line agent) and to emphasize using the recommended ASD doses.

As part of its development of SE Guidelines, the Neurocritical Care Society conducted an international survey of SE experts because of a lack of evidence-based research in SE [85]. Lorazepam was considered the drug of choice for initial therapy in all age groups.

The following ASDs are available in IV preparations and have been used as second and third-line therapy.

IV valproic acid is given in an initial loading dose of 20–40 mg/kg [86–89]. An additional 10 mg/kg is given 10 min after the loading dose if the seizure continues [90]. The infusion rate is from 3 to 6 mg/kg/min [91]. Adverse effects include hypotension, and hepatopathy (hyperammonemia) and pancreatopathy (elevated amylase and lipase), which may be seen acutely. Thrombocytopenia occurs, but usually with chronic administration. A randomized clinical trial of phenobarbital versus sodium valproate for the initial treatment for SE in children demonstrated seizure termination in 90% with sodium valproate versus 77% with phenobarbital, with significant adverse effects seen in 74% with phenobarbital versus only 24% with valproate [92].

Levetiracetam: the recommended loading dose ranges from 20 to 60 mg/kg. A typical dose for responders is 30 mg/kg, with infusion rates of 2–5 mg/kg/min [93, 94]. Loading doses of 50 mg/kg [95] and 60 mg/kg [96] have been used without significant side effects. In one study, the

Table 27.9 American Epilepsy Society Guideline for Treatment Status Epilepticus [6, 7]

Initial therapy of choice: a benzodiazepine (level A)
IV lorazepam, 0.1 mg/kg/dose, maximum 4 mg, may repeat once (level A)
IV diazepam, 0.15–0.2 mg/kg/dose, maximum 10 mg, may repeat once (level A)
IM midazolam, 0.2 mg/kg/dose; 10 mg for >40 kg, 5 mg for 13–40 kg, single dose (level A)
If none of these is available:
IV phenobarbital, 15 mg/kg/dose, single dose (level A)
Rectal diazepam, 0.2–0.5 mg/kg, maximum dose, 20 mg/dose, single dose (level B)
Intranasal or buccal midazolam, 0.2 mg/kg, maximum 10 mg (level B)
If seizures continue: choose one of the following second-line agents and give single dose
IV fosphenytoin, 20 mg PE/kg, maximum 1500 mg PE/dose (level U)
IV valproic acid, 40 mg/kg, maximum 3000 mg, single dose (level U)
IV levetiracetam, 60 mg/kg, maximum 4500 mg, single dose (level U)
Or IV phenobarbital, if not previously given
If seizures continue, no clear evidence to guide (level U)
Anesthetic doses of thiopental, midazolam, pentobarbital or propofol
Some protocols in children: use midazolam first; starting at 0.2 mg/kg/dose, maximum 10 mg. If seizures continue for another 5 min, another 0.2 mg/kg and start infusion of 0.1 mg/kg/h; if seizures continue, another 0.2 mg/kg/dose and increase infusion to 0.2 mg/kg/h. If seizures continue, repeat midazolam, 0.2 mg/kg/h and start pentobarbital, 5 mg/kg, followed by infusion of 1 mg/kg/h, increase as needed to 3 mg/kg/h (2)

Level ratings: *Level A* One or more class I studies or two or more consistent class II studies; *level B* one or more class II studies or three or more consistent class III studies; *level U* lack of studies meeting level A, B, or C designation. *IM* intramuscular, *IV* intravenous, *PE* phenytoin equivalents

loading dose was given over 5–6 min [96]. Minor reactions include lethargy, fatigue, restlessness, and pain at the infusion site. Very high doses (240 mg/kg/day) have been used with good efficacy and limited adverse effects, with one child having an increase in seizures [97]. Adverse effects include agitation and behavior problems. Levetiracetam dosing must be adjusted for renal failure and is adjusted based on the glomerular filtration rate (GFR).

In a study of 88 children with ARS or SE, a comparison of IV phenobarbital, at a median loading dose of 20 mg/kg, versus IV levetiracetam, at a median loading dose of 30 mg/kg, led to seizure termination in 58% with levetiracetam versus 74% with phenobarbital [98]. A 30 mg/kg loading dose of levetiracetam is now considered low [99, 100].

Lacosamide is now available in IV formulation. In adults, a 200–400 mg IV loading dose has been used most often, although 50, 100, 150, and 300 mg doses have been used. One study in adults used an infusion rate of 40–80 mg/min, and 15 min is now suggested for the infusion time [101–103]. In a pediatric case report, 25 mg BID controlled refractory SE after 24 h [104]. Adverse effects include first-degree heart block and hypertension, so lacosamide should be used with caution in patients with known cardiac conduction problems [105]. In a study using lacosamide for refractory SE in 9 children, the mean loading dose was 8.7 mg/kg, with a range of 3.3–10 mg/kg; the average dose in the first 24 h was 13.8 mg/kg. For the loading dose, 7 of 9 patients received 10 mg/kg [106].

The patient's condition, the type of SE, and the underlying epileptic syndrome must be taken into consideration when deciding how aggressive management should be. For example, the child with an acute brain insult and SE is more prone to brain injury than the child with absence SE in the setting of childhood absence epilepsy. The sequence of ASDs used for juvenile myoclonic epilepsy may differ from that used for symptomatic generalized SE. For patients with recurrent seizures or nonconvulsive seizures in the setting of chronic epilepsy with stable vital signs, less aggressive treatment should be considered. The risk of ongoing brain injury is less likely in the setting of chronic epilepsy, unless there is an acute precipitant (i.e., acute on chronic or remote symptomatic with an acute precipitant).

The Neurocritical Care Society Survey indicated that after failure of the first two agents, midazolam, pentobarbital, and propofol are used earlier in adults than in children [85]. This follows the previously recommended protocols. Research in pediatric SE has been increasing, in part based on the need for evidence-based treatment and management. Treatment studies now include children. In the Rapid Anticonvulsant Medication Prior to Arrival Trial (RAMPART), a phase 3 non-inferiority study, intravenous lorazepam was compared to intramuscular midazolam (MDZ); IM MDZ was at least as safe and effective as IV lorazepam [107]. A current study,

the Established Status Epilepticus Treatment Trial (ESETT), plans to determine the second-line agent to use after failure of the initial benzodiazepine, comparing IV fosphenytoin at 20 mg/kg, IV levetiracetam at 60 mg/kg, or IV valproic acid at 40 mg/kg, in patients older than 2 years of age [26, 108, 109].

High-quality data are needed to develop evidence-based treatment strategies for pediatric SE to improve management and prognosis. The Pediatric SE Research Group (pSERG) was established for the purpose of collecting data prospectively from multiple centers [110]. Although in general, randomized clinical trials are preferred, prospective observational study protocols using a comparative effectiveness approach may be more feasible.

The pSERG has evaluated time-based treatment, evaluating the elapsed time from the onset of pediatric CSE to the administration of ASD [111]. The first, second, and third ASD doses were administered at a median time of 28 min (range: 6–67 min), 40 (20–85), and 59 (30–120) min after SE onset. Even in the inpatient setting, the first and second ASDs were given at 8 (5–15) min and 16 (10–40) min after SE onset. This study is quite revealing, demonstrating that despite the many guidelines recommending that the initial ASD should be administered quickly, this has not yet happened.

There are rare genetic disorders of pyridoxine (vitamin B6) metabolism (pyridoxine responsive and pyridoxine resistant) that may result in SE. Therefore, IV pyridoxine administration is recommended for refractory SE in the infant and younger child, less than 3 years of age [112]. The dose is 30 mg/kg.

Pre-hospital Treatment of Status Epilepticus

The premonitory or incipient stage of SE can now be treated in a pre-hospital setting with rectal, buccal, or nasal ASDs, and IV ASDs are now given in the field. A prospective pre-hospital treatment study in adults randomized IV 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 versus 43% response with diazepam, versus a 21% response to placebo ($P = 0.001$)] [113]. A retrospective study of CSE in children ($n = 38$) showed that pre-hospital treatment with (0.6 mg rectal) diazepam resulted in a shorter duration of SE than occurred in children who received no pre-hospital treatment (32 min vs. 60 min) and less seizure recurrence in the emergency department (58% vs. 85%), and there was no difference in intubation rates [114]. Rectal diazepam gel is now established care at home for SE or serial seizures. The maximum dose is 10 mg in children, determined by age and weight. Although not FDA-approved for SE, we use it for SE in the home, but we do not consider it appropriate for inpatient use except under certain conditions, such as lack of IV access, or in the epilepsy monitoring unit when no IV has been placed in advance.

Several other routes are used for benzodiazepines when there is no IV access. Sublingual lorazepam [115] or intranasal or buccal midazolam [116] can be given, with rapid buccal absorption documented by levels [117]. Intranasal midazolam (0.2 mg/kg) has equal efficacy with IV diazepam (0.3 mg/kg) for prolonged febrile seizures [118], and buccal midazolam (10 mg) and rectal diazepam (10 mg) have shown equal efficacy for seizures greater than 5 min [117]. ASDs may also be given by an intraosseous infusion. We have been using more intranasal (IN) midazolam now for the home treatment of seizures, ARS, and SE, especially in the older child. An IN dose of MDZ achieves a greater serum level at 5 min than does an IM dose [119]. A 0.2 mg/kg dose of IN midazolam is equivalent to 0.5 mg/kg of diazepam [120]. Local mucosal irritation occurs in about 1/3 of cases and respiratory depression in 1%. Intraosseous lines can provide rapid access when IV access is difficult to achieve.

A systematic review and meta-analysis of convulsive seizure treatment without IV access showed that buccal MDZ was superior to rectal DZP and that intranasal LZP was equivalent to IV LZP (with high-quality evidence); intranasal MDZ was superior to rectal DZP (with low-quality evidence) [121].

Special Syndromes of Status Epilepticus

Specific epilepsy syndromes have sleep-activated epileptiform activity occurring continuously, that mimic electrographic status epilepticus [2, 7, 122, 124]. These are considered special syndromes of NCSE [2]. The new classification of SE considers these as ‘indeterminate conditions,’ or ‘boundary syndromes’ of SE [8]. This sleep-activated epileptiform activity is referred to as electrical status epilepticus of sleep (ESES) or continuous spike waves of slow sleep (CSWS) [122–125].

These syndromes are considered epileptic encephalopathies, defined as disorders in which the epileptiform activity itself may contribute to severe cognitive and behavioral impairments above and beyond what might be expected from the underlying pathology alone (such as a cortical malformation); these impairments can worsen over time [126]. Clinical manifestations caused by the epileptiform activity include cognitive and behavioral dysfunction, motor dysfunction, or regression in cognitive function, with clinical improvement noted if the epileptiform activity can be decreased. This epileptiform activity may also represent an epiphenomenon, meaning that the EEG activity is caused by the underlying etiology but is not the cause of the

neurologic dysfunction, and even if the spikes are eliminated, the dysfunction continues because the underlying cause persists. For treatment purposes, determining the overall amount (referred to as prevalence in the updated classification [8]) of epileptiform activity present is important, as the greater the amount of epileptiform activity, the more likely it is to interfere with cortical functioning. The concept of an epileptic encephalopathy has changed our management of epileptiform activity on the EEG. Earlier, we were taught "Treat the patient, not the EEG," with the implication that we should treat seizures but not interictal epileptiform EEG activity [7]. This old teaching (which did not recognize that an epileptic encephalopathy results in dysfunction due to the actual spikes and not from the clinical seizures only) has now been revised.

The epileptic encephalopathy syndromes include early myoclonic encephalopathy (neonatal myoclonic encephalopathy), early infantile epileptic encephalopathy (Ohtahara syndrome), infantile spasms (now, 'epileptic spasms'; West syndrome), Dravet syndrome, myoclonic status in non-progressive encephalopathies, the Lennox–Gastaut syndrome, and myoclonic-atonic epilepsy (Doose syndrome) [126]. These syndromes typically have frequent seizures.

Of these epileptic encephalopathies, the Landau–Kleffner syndrome (LKS) and continuous spike waves of sleep (CSWS) have rare or even no overt clinical seizures. Both are characterized by regression in cognitive abilities, either the language regression seen predominantly in LKS [125–127] or a more global neuropsychiatric regression in CSWS [123, 124]. Both have marked sleep activation of epileptiform activity on EEG. Indeed, this activation is required to make the diagnosis. Patry defined the term "electrical status epilepticus of sleep" as having sleep-activated epileptiform activity in greater than 85% of slow-wave sleep [123]. Veggiotti et al. [128] emphasized the difference between the EEG pattern of CSWS and the epileptic syndrome of CSWS. Not all patients with a sleep-activated pattern consistent with ESES have the age-related epileptic syndrome of LKS or CSWS. Here, we use the term ESES to describe the EEG and CSWS to describe the epileptic syndrome.

LKS is rare, representing only 0.2% of pediatric epilepsies [129]. Its onset is usually in children older than 4 years of age [130] and may manifest first as an apparent word deafness, a verbal auditory agnosia. Seizures and behavior disturbances, particularly hyperactivity, each occur in about two-thirds of children with LKS [125]. The majority of LKS cases are idiopathic, but any pathologic process affecting auditory cortex may cause LKS. Neuroimaging is necessary because 'symptomatic' LKS cases occur. We have seen a child 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) [124].

In LKS, classic features 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 the classic features of LKS, but with the sleep-activated epileptiform EEGs, have been referred to as LKS variants [131]. The variants include children with involvement of more anterior language areas with dysfunction characterized by oral-motor apraxia, sialorrhea, seizures, and an abnormal EEG (centrotemporal spikes similar to those seen with benign focal epilepsy); children with pervasive developmental disorders (PDD, especially autism) with language regression and abnormal EEGs; and even children with congenital aphasias, also called developmental language disorders, with epileptiform EEGs.

The LKS evaluation includes a baseline history, physical examination, sleep-deprived EEG, a formal neuropsychologic evaluation, neuroimaging, with MRI preferred, long-term video EEG monitoring if needed, functional neuroimaging with either SPECT or PET scan, and frequency-modulated auditory evoked responses (FM-AER). The FM-AER is an evoked response that tests receptive language function, and is usually absent with a verbal auditory agnosia [132, 133]. All LKS children need intensive speech therapy.

Landau and Kleffner reported a positive relationship between ASD treatments and improvement of the aphasia [126]. In 1967, Deuel and Lenn reported a case with a clear relationship between ASD treatment and language improvement [134]. Carbamazepine and valproate were widely used. We were using valproic acid because it is an 'anti-epileptogenic' agent that suppresses spikes, but 'epileptogenic' truly refers to suppression of the development of epilepsy—or the underlying process that leads to epilepsy [135]. A spike suppressor may actually 'normalize' the EEG. Carbamazepine may worsen generalized epilepsies and may even worsen focal spike and wave discharges, with a resultant increase in epileptiform activity on the EEG [136, 137]. Lamotrigine is also a good spike suppressor [138]. Unfortunately, we have seen at least some children worsen with any ASD used.

The LKS prognosis varies. The original LKS patients were followed up by Montovanni and Landau in 1980 [139]. Among their nine patients, with follow-up from 10 to 28 years, four had full recovery, one a mild language disability, and four had moderate disability. Others have not had as positive an outcome. Bishop did a literature review of patients with LKS, identifying 45 patients. Age of onset was

related to outcome: outcome was less favorable if onset occurred before 4 years of age [130]. Deonna et al. [140] reported that only one of seven adult patients had normal language, with the six others demonstrating varying degrees of language deficits, some with complete absence of language. In the neuropsychologic follow-up of 12 patients, Soprano et al. [141] reported persistent language deficits of different degrees in 9 of 12 cases.

Continuous Spike Waves of Sleep (CSWS, ESES)

Electrical status epilepticus of sleep, or CSWS, is also rare, occurring in 0.2% of pediatric epilepsies [129]. Strict definition of ESES requires sleep-activated epileptiform activity in 85% of slow-wave sleep [123–125]. Symptomatic and cryptogenic cases occur, these determined by the identification of a specific etiology and whether neurologic and psychomotor development was normal before the onset of CSWS.

Children with CSWS and ESES commonly have seizures, but they may be infrequent. The hallmark of CSWS is regression in cognitive functioning and behavior, but not primarily a language deterioration as occurs in LKS. Tassinari reported 29 children with CSWS [125]. All except one child 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 earlier normal development, all had severe loss of intelligence quotient (IQ) and behavioral disturbances, defined as decreased attention span, hyperactivity, aggression, 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 marked hyperactivity, and one showed 'massive regression,' including in language, and a loss of interest in all activities.

The epileptic syndrome of CSWS is distinguished from the EEG finding of ESES: ESES describes the sleep-activated EEG, whereas the epileptic syndrome CSWS includes ESES plus the characteristic clinical manifestations [128]. For example, the ESES pattern may occur in LKS, but it is predominantly the language deterioration that characterizes the LKS syndrome. The clinical manifestations of a syndrome may depend on the location of the epileptiform activity. With a more focal ESES, language regression may predominate, whereas neurobehavioral dysfunction may predominate with more generalized EEG abnormalities [142]. LKS and ESES have been considered 'benign' syndromes because the EEG may improve over time, but given the devastating neuropsychologic deficits occurring in an epileptic encephalopathy, we consider these 'malignant' epileptic syndromes.

The EEG in LKS shows bilateral or multifocal spikes and spike and wave discharges, occurring usually in the posterior regions, especially the temporal or parietal regions, with a marked activation during non-REM sleep (Fig. 27.1), but discharges occur in many locations and may even be generalized [124].

Some experts require ESES to diagnosis LKS, but not every EEG in children with LKS has ESES. The EEG may improve over time, either spontaneously or with treatment [143, 144]. The EEG abnormalities in LKS may also be an epiphenomenon [145]. The spike-wave index may reach only 50% in some LKS [146].

The degree of spike activation required to diagnose ESES varies and several parameters are used to determine this. The original paper by Patry et al. [123] described 'continuous' as EEG abnormalities (spikes) occupying at least 85% of slow sleep. Our group has considered a 50% increase or greater in epileptiform activity in sleep (compared to in the waking state) as the criterion for diagnosis [147], using the spike-wave percentage, analogous to the spike-wave index, which has been defined loosely [148]. The spike-wave index or spike-wave percentage refers to the number of one second bins with spikes in non-REM sleep compared to the total number of one second bins. In ESES, sleep activation occurs in drowsiness rather than in slow sleep [149]. Rather than the "continuous spike wave during slow sleep" as originally used for the syndrome, the term used now is "epileptic encephalopathy with continuous spike-and-wave during sleep (CSWS)" [3]. There is also the spike frequency, which refers to the number of spikes in 100 s. The spike-wave percentage and spike frequency correlate with each other, but the spike frequency may provide more detail, as there is no 'ceiling effect' [149].

We quantify the amount (prevalence) of epileptiform activity by visual inspection on each clinical EEG using the following standard definition for EEG terms rare, occasional, frequent, abundant, or continuous: 0–1% spikes is rare; 1–10% spikes, occasional; 10–50% spikes, frequent; 50–90% spikes, abundant, and greater than 90%, continuous [7]. With practice, this can be determined rapidly during the actual EEG interpretation.

Guilhoto and Morrell reported that spike location may determine the epilepsy syndrome. With a more focal ESES pattern, LKS with language regression was the predominant syndrome, whereas when the ESES pattern was more generalized, the CSWS syndrome with generalized neurobehavioral dysfunction was predominant [142]. Guilhoto et al. [150] subsequently reported 17 children with ESES. Five had LKS, and the EEG showed diffuse abnormal activity with accentuation in the centrotemporal region, whereas the other patients had widespread discharges. We recently showed that there are no differences in the clinical features of those with focal versus generalized ESES [151].

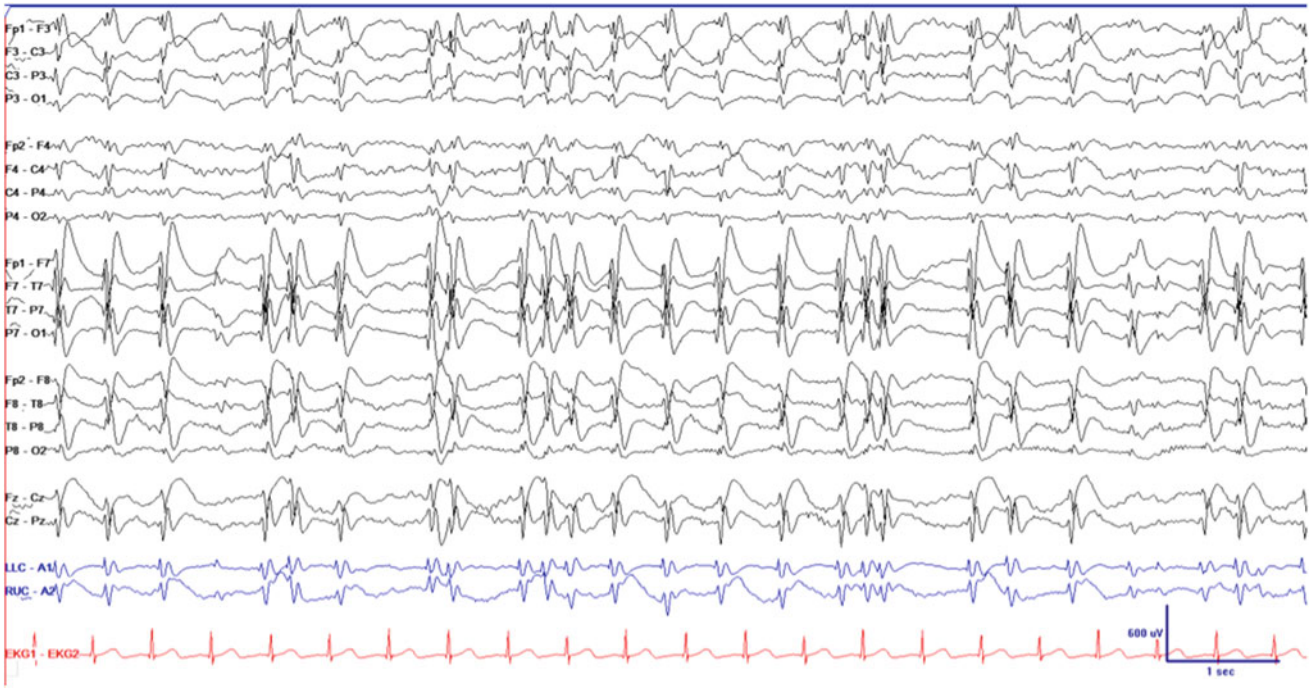

Fig. 27.1 Electrical status epilepticus of sleep in Landau–Kleffner syndrome. Discharges maximal in the left temporal–parietal region

Treatment of both syndromes, LKS and CSWSW, is similar, but the specifics are debated. Although there was a relationship between ASD treatment and aphasia improvement in the original LKS report [127], it is now thought that ASDs control seizures but do not ameliorate the aphasia [152, 153]. McKinney and McGreal [154] reported a better response with steroids. Some children who had not responded to ASDs have improved after steroid therapy [152, 153]. The rapidity of the response and sequelae may depend on the duration and severity of symptoms prior to treatment. High initial doses are more effective, and brief treatment is often ineffective or leads to a high relapse rate.

The most successful ASDs for ESES are valproic acid, benzodiazepines, and ethosuximide [125]. As above, carbamazepine may worsen the EEG [136, 137]. We have seen children treated with carbamazepine for seizures with focal epileptiform abnormalities on EEG who subsequently developed language regression and then evolved into ESES. For treatment, we use ASDs with anti-epileptogenic properties as first-line for ESES. Albaradie et al. [155] retrospectively analyzed our experience with ESES treatment in 12 children. Only 1 of 12 responded to initial short-term therapy with VPA.

Levetiracetam has good efficacy for ESES and LKS. Kossoff et al. [156] reported a clinical and EEG response to levetiracetam at 60 mg/kg. Abey et al. [157] reported improvement in 7 of 12 children treated with levetiracetam at 50 mg/kg/day. In a multicenter study, Chen et al. [158] reported that ESES disappeared in 41 of 73 patients (56%) treated at doses from 30 to 60 mg/kg, with a better response seen in the idiopathic group. From one institution, a positive EEG response to levetiracetam at 30–50 mg/kg/day was found in 32 of 71 children (45%), with a relapse in 8 (25%) of the initial responders [159]. The efficacy of levetiracetam may be greater in those with a symptomatic etiology [160].

Lacosamide has been shown recently to control EEG epileptiform activity in eight children with CSWS. With lacosamide titrated to 12.2 mg/kg/day, 75% of patients were responders; three had normal EEGs, but two initial responders relapsed [161]. Fine et al. [162] used acetazolamide, a carbonic anhydrase inhibitor, at an initial average dose of 10–20 mg/kg/BID in two divided doses in six children; 3 of 6 patients had a spike-wave index of 0% following therapy.

If ASDs do not work for LKS, CSWS, or ESES, then either high-dose diazepam or corticosteroids may be helpful. High-dose corticosteroids may work through their GABAergic effects rather than by immune mediation [163]. De Negri et al. [164] introduced a high-dose diazepam protocol for electrical status epilepticus (ESE). They used a rectal dose of 1 mg/kg, with EEG monitoring, and continued a dose of 0.5 mg/kg orally for several weeks only in those who had an initial EEG response. Patients on chronic benzodiazepine treatment did not respond as well. When a clinical relapse occurred, a 1 mg/kg dose was repeated. Only

one child had LKS and one had ESES. We modified this high-dose diazepam protocol, using 1 mg/kg orally under EEG guidance, and subsequently treated all children with a dose of 0.5 mg/kg orally for three to four weeks [165]. If the follow-up EEG at three to four weeks showed no improvement, we tapered the diazepam rapidly. If the EEG showed improvement, we tapered slowly, by 2.5 mg/month. In our series, every child who responded initially and then had a rapid diazepam taper had either a clinical or electrographic regression. We now continue a maintenance diazepam dose, usually at a dose of 2.5–10 mg, depending upon weight, and based on tolerability, for 2 years.

Sánchez Fernandez et al. [166, 167] reported on both the short-term and long-term responses to high-dose diazepam given at 1 mg/kg (maximum 40 mg) orally for one night and then subsequently treated with 0.5 mg/kg (maximum 20 mg) daily. Although the long-term response is predicted by the short-term response [167], this is not absolute. We have seen several patients with initial clinical improvement without EEG improvement in whom we continued treatment, and who subsequently had delayed EEG improvement. The best long-term responders to high-dose diazepam are those with idiopathic LKS.

Steroids have long been used for pediatric epilepsy, especially for infantile (epileptic) spasms [168], and the early use of high-dose oral corticosteroids is recommended for LKS and CSWS [152–155]. We have used daily prednisone for 6 months in six children with the dose schedule outlined in Table 27.10 [169]; 5 of 6 had a positive response but 4 of 5 patients (80%) relapsed and required another course [155]. Before the elective use of corticosteroids, immunizations should be up to date.

The early use of IV followed by oral steroids has been recommended to achieve a faster response than with oral steroids alone. Tsuru et al. [170] reported two children with LKS treated with high-dose IV methylprednisolone (20 mg/kg/daily) infusions for three consecutive days, followed by three subsequent infusions separated over four days, followed by oral prednisolone, 2 mg/kg daily. Buzatu et al. [171] treated 44 children with CSWS with oral hydrocortisone, at 5 mg/kg daily for the first month, 4 mg/kg the second month, and 3 mg/kg the third month. Complete seizure control occurred in 33 of 41 patients, and the EEG became normal in 21 children [171]. Relapse occurred in 14 children, in six during the steroid trial, and eight relapsed 6–12 months after treatment stopped. Pulse steroid therapy may decrease the adverse effects of steroid treatment [172–174] (see Table 27.10). We now try pulse steroid dosing first, possibly followed by daily dosing depending upon the response.

The rapid control of clinical seizures and epileptiform activity may provide the best cognitive outcome. The decision of how aggressively to treat ESES is based on three factors: seizure control, the abundance of epileptiform activity, and the neuropsychologic profile, especially if regression is present. More aggressive therapy is warranted when regression occurs and the ESES is persistent. Conversely, if there is no regression, more aggressive therapy may not be needed [175].

The various agents used to treat ESES have been assessed in several large studies. Inutsuka et al. [176] studied the following treatments in 15 children: (1) sodium valproate (VPA) to a level greater than 100 mg/L; (2) the combination of VPA plus ethosuximide; (3) short cycles of high-dose diazepam; or (4) intramuscular ACTH. Treatment with short cycles of ACTH (for 11–43 days) or diazepam (DZP) (6–7 days) did not achieve long-term remission, whereas either high-dose VPA alone (n = 7) or VPA in combination with ethosuximide (n = 3) achieved remission in ten children (67%). In 30 children with ESES duration of 2–60 months [36], Kramer and colleagues reported efficacy of steroids in 65%, levetiracetam in 41%, clobazam in 31%, sulthiame in 17%, and immunoglobulins in 37%; there was no efficacy for valproic acid, lamotrigine, topiramate, or ethosuximide. High-dose diazepam had a 37% efficacy, but all these patients relapsed when it was stopped [177]. In 117 children, Caraballo et al. [178] suggested that ethosuximide, clobazam, or sulthiame might be best for the EEG, as might

Table 27.10 Daily prednisone dose for Landau–Kleffner syndrome, continuous spike waves of sleep, and electrical status epilepticus of sleep [169, 174]

Treatment period	Dose	Frequency
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
Intravenous pulse steroid dose		
Methylprednisolone, 20 mg/kg/day daily for 3 days		
Methylprednisolone, 20 mg/kg/day monthly for 5–6 months		

Table 27.11 Initial therapy to control electrical status epilepticus as rapidly as possible [124, 183]

Non-lesional cause
Clobazam, for 3 months; if this does not work, follow with corticosteroids
Corticosteroids
First: pulse IV methylprednisolone (20 mg/kg/day for 3 days) and monthly for 5–6 months; followed by either ethosuximide or levetiracetam
If only partial response or adverse effects preclude ongoing therapy, clobazam plus ethosuximide, or sulthiame, or levetiracetam
Symptomatic/lesional cause
Corticosteroids initially; refer to above

valproic acid and ethosuximide together; if these do not work, corticosteroids should be considered early. In 59 children with both idiopathic and structural or symptomatic cases [179], Arhan and colleagues reported that clobazam, levetiracetam, IV steroids, and IVIG were successful, although mostly used in combination. Albaradie et al.[155] retrospectively analyzed our experience with ESES treatment in 12 children; only 1 of 12 responded to initial short-term therapy with VPA. We have used combined high-dose benzodiazepine and pulse steroid therapy when regression continued [180].

van den Munckho et al. [181] performed a literature review of 575 children with ESES in order to assess treatment. ASDs led to improvement in 49%, benzodiazepines in 68%, and steroids in 81%. In the subgroup of consecutively treated patients, ASDs led to improvement in only 34%, benzodiazepines in 59%, and steroids in 75%. Cognitive improvement occurred in 40% with ASDs, 50% with benzodiazepines, and 78% with steroids, and EEG improvement occurred in 45% with ASDs, 59% with benzodiazepines, and in 70% with steroids.

There have been no randomized clinical trials for LKS, CSWS, or ESES, so treatment recommendations are from case series and expert opinion. A trial of high-dose clobazam is ongoing in the US and a trial of clobazam versus corticosteroids is beginning in Europe. Fernandez et al. [182] recommend either standard ASDs, benzodiazepines, or corticosteroids as first-line therapy, depending upon the patient and physician discretion. Veggiotti et al. [183] recommend controlling ESES as rapidly as possible in order to improve cognitive outcomes. Initial treatment is determined by etiology: in the non-lesional or unknown cases, they use 3 months of clobazam, followed by steroids if the clobazam does not work. In the lesional or symptomatic cases, they start with pulse corticosteroid therapy followed by surgery, if appropriate (Table 27.11). For pulse therapy, IV methylprednisolone is given at 15–30 mg/kg/day for three days once a month, for 4 months [184]. Pulse therapy has fewer adverse effects than daily therapy.

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Status Epilepticus in Critically Ill Children

28

Diana J. Walleigh, Douglas M. Smith, Emily L. McGinnis, and Nicholas S. Abend

Introduction

Status epilepticus (SE) is a common neurologic emergency in pediatric intensive care units [1, 2], but management is highly variable and treatment delays are common [3–6]. Additionally, many seizures in critically ill children are electrographic-only, so continuous electroencephalographic (C-EEG) monitoring is required for seizure identification. This chapter reviews the identification and management of SE in critically ill children.

Status Epilepticus Management Overview

Status epilepticus refers to a prolonged seizure or recurrent seizures without a return to baseline. It is a common pediatric neurologic emergency, with an incidence of 18–23 per 100,000 children per year [7]. The clinician's aims are to rapidly and simultaneously 1. stabilize the patient medically, 2. identify and manage precipitating conditions, and 3. terminate clinically evident and electrographic-only seizures.

Historically, SE was defined as a seizure lasting longer than 30 min or a series of seizures without return to baseline level of alertness between seizures [8]. The *prodromal or incipient stage* is in the first 5 min, during which it is unknown whether the seizure will terminate on its own or evolve into SE. The next period is divided into *early* SE (5–30 min), *established* SE (>30 min), and refractory SE (*RSE*) (seizures persisting despite treatment with adequate doses of 1 or 2 anti-seizure medications). The temporal definition of SE has gradually shortened due to increasing recognition that most seizures are brief (3–4 min) [9] and that delays in administration of anti-seizure drugs (ASDs) are associated with more refractory seizures [10–14]. The terminology related to SE duration has been modified to convey a greater sense of urgency. Thus, the Neurocritical Care Society's (NCS) Guideline for the Evaluation and Management of SE in children and adults defines SE as 5 min or more of continuous clinical or electrographic seizure activity or both, or recurrent seizure activity without recovery (returning to baseline) between seizures. The guideline recommends that definitive control of SE be established within 60 min of onset. RSE is defined as clinical or electrographic seizures that persist after an adequate dose of an initial benzodiazepine and a second appropriate ASD. In contrast to prior definitions, there is no specific time that must elapse before initiation of RSE management if prior drugs have not terminated seizures. The timing of medical interventions to stabilize the patient and identify any underlying precipitant is categorized as "immediate," which roughly corresponds to that of incipient SE. ASDs are classified as "emergent," "urgent," or "refractory." "Emergent" interventions correspond with the temporal definitions of early SE, and urgent interventions with established SE [15].

The American Epilepsy Society's (AES) Guideline for SE Management follows the 5 min definition without subdividing based on seizure type. It suggests that management be considered in an "initial therapy phase" (5–20 min), a "second therapy phase" (20–40 min), and a "third therapy phase" (40–60 min) [16].

The International League Against Epilepsy defines SE as a condition resulting either from the failure of the mechanisms responsible for seizure termination or from the initiation of mechanisms which lead to abnormally prolonged seizures (after "time point t_1") and can have long-term consequences (after "time point t_2"), including neuronal death, neuronal injury, and alteration of neuronal networks, depending on the type and duration of seizures. These time points were defined depending on whether the seizure was

D.J. Walleigh · D.M. Smith · E.L. McGinnis · N.S. Abend (✉)
Division of Neurology, Departments of Neurology and Pediatrics, The Children's Hospital of Philadelphia, The University of Pennsylvania, Philadelphia, PA, USA
e-mail: abend@email.chop.edu

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Table 28.1 International League Against Epilepsy definition of status epilepticus indicates that emergency treatment of status epilepticus should be started at T1 and long-term consequences may occur at T2

Type of status epilepticus	Time 1 (Treatment started) (min)	Time 2 (Consequences expected)
Tonic-clonic	5	30 min
Focal with impaired consciousness	10	>60 min
Absence	15	Unknown

Adapted from Trinka et al. [17]

generalized tonic-clonic SE, focal SE with impaired consciousness, or absence SE (Table 28.1) [17].

There are various approaches to SE management, and treatment delays are common. Studies of pediatric SE management in emergency departments have reported that laboratory parameters were often not checked and some results were available only after long delays [6]; 23% of children received benzodiazepine dosing outside usual dosing guidelines [6]; the median time before a second-line ASD was administered was 24 min [18]; and substantial delays in ASD administration were common in children with RSE [3]. As RSE is often managed in the ICU, it is particularly noteworthy that a multi-center study of SE and RSE from multiple large pediatric centers in the United States reported that the median time from seizure onset to medication administration was 28 min for the first ASD, 40 min for the second ASD, and 59 min for the third ASD. The first and second non-benzodiazepine ASDs were administered at a median of 69 and 120 min (Fig. 28.1) [3]. These data indicate that delays may occur during the transition from emergency department care for initial SE to the ICU for RSE management with pharmacologic coma-inducing medications.

Delays in ASD administration are problematic because several studies have described associations between SE management delays and more prolonged seizures [10] and lower ASD responsiveness [11–14]. A study of children with convulsive SE (CSE) found that for every minute delay between SE onset and emergency department arrival, there was a 5% increase in the risk of having SE last >60 min [10]. Another study of children with continued clinical seizures after the first and second-line ASDs reported that seizures were terminated in 100% of subjects when a third medication was administered within one hour but in only 22% when the third medication was administered after one hour [11]. A study of children documented that the first-line and second-line medications terminated CSE in 86% of children when administered in less than 15 min but in only 15% of children when administered after ≥30 min [12]. Another study of children with convulsive seizures lasting >5 min found that treatment delays of >30 min were associated with delays in seizure control [13]. Finally, midazolam efficacy has been found

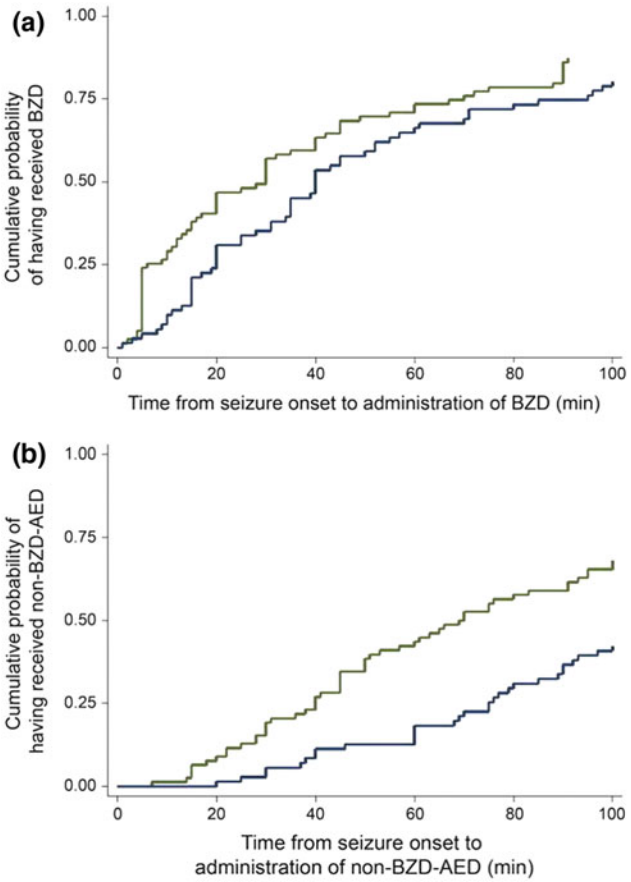

Fig. 28.1 Kaplan–Meier curves show the time from SE onset to anti-seizure drug *ASD* administration. Top shows benzodiazepine *BZP* administration (*first = green; second = blue*). *Bottom* shows non-BZP administration (*first = green; second = blue*). (From Sánchez Fernández et al. [3], with permission.)

significantly lower when treatment was initiated >3 h after seizure onset, and there was a trend toward reduced efficacy even at one hour [14].

To expedite therapeutic decisions, a consensus document recommended that all units have a written SE management pathway with a clearly structured time frame [19]. Several examples have been published [15, 16, 20–22], but they may need to be adapted based on local resources and practice. A 2010–2011 survey of Emergency Departments in Illinois

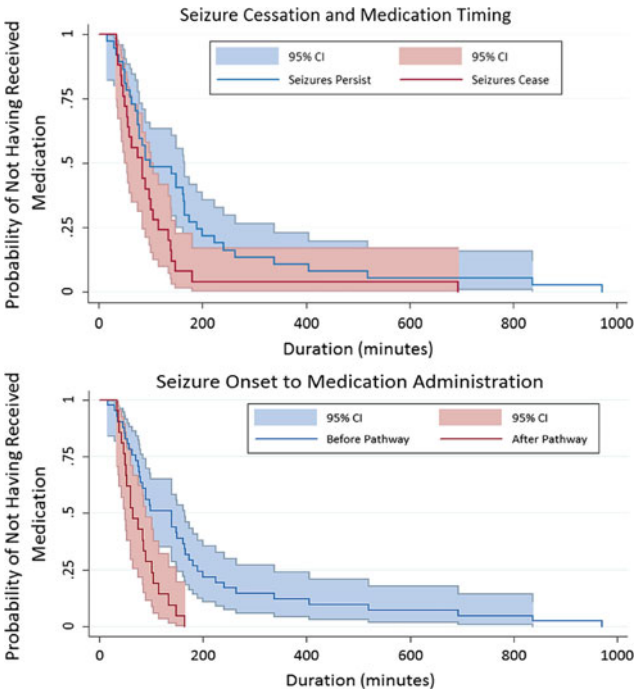

Fig. 28.2 (*Bottom*) Kaplan–Meier survival curve comparing patients before (*blue*) and after (*red*) implementation of an ICU EEG monitoring pathway for the duration from electrographic seizure onset to initial anti-seizure medication administration. (*Top*) Kaplan–Meier survival curve comparing patients in whom seizures persist (*blue*) or cease (*red*) after initial anti-seizure medication was administered. (From Williams et al. [24], with permission.)

obtained responses from 88% of 119 facilities and reported that only 19% had a management protocol for SE, and only 9% had a pediatric-specific SE protocol [23].

Given the observed delays in ASD administration even in patients with RSE managed at large pediatric centers, several strategies for reducing that delay have been proposed (Fig. 28.2) [24]. Delays are also common in the management of electrographic-only seizures, as identified by continuous EEG (C-EEG). Data collected at a quaternary hospital demonstrated that the median duration from electrographic seizure onset to initial ASD administration was 139 min (interquartile range (IQR): 71–181 min). After implementation of a pathway that standardized management, provided staff education and streamlined communication, the median duration was significantly shorter, at 64 min (IQR: 50–101 min). Seizure cessation after administration of an initial ASD was more common in the pathway than in baseline group (67% vs. 27%), and patients with seizure cessation after the initial ASD were more likely to have received the medication faster than those without seizure cessation (Table 28.2).

Medical Stabilization and Etiology Diagnosis

While most of this chapter focuses on seizure management, two important overall management components that must occur simultaneously are medical stabilization and identification of precipitating etiologies requiring specific therapy.

The NCS's guideline provides a timed treatment pathway [15]. Steps in the initial 2 min include non-invasive airway protection and with head positioning, and vital sign assessment. Steps in the initial 5 min include neurologic examination and placement of peripheral intravenous access for administration of 'emergent' ASDs and fluid resuscitation. Steps in the initial 10 min include intubation if airway or gas exchange is compromised or intracranial pressure is elevated. Intubation may be necessary because of seizure associated hypoventilation, medication associated hypoventilation, inability to protect the airway, or other causes of oxygenation or ventilation failure. Steps in the initial 15 min include vasopressor support if needed [15].

Multiple studies have characterized the various etiologies for SE [7, 25–27]. Acute symptomatic conditions are identified in 15–20% of children with SE [7, 26, 28]. Rapidly reversible causes of seizures should be diagnosed and treated rapidly, e.g. with hypoglycemia, hyponatremia, hypomagnesemia, and hypocalcemia. The American Academy of Neurology's (AAN) practice parameter on the Diagnostic Assessment of the Child with SE reported that abnormal results among children who underwent testing included low ASD levels (32%), neuroimaging abnormalities (8%), electrolyte abnormalities (6%), inborn errors of metabolism (4%), ingestion (4%), central nervous system infections (3%), and positive blood cultures (3%) [29]. The NCS's guideline provides suggestions regarding etiologic testing including bedside finger stick blood glucose (0–2 min) and serum glucose, complete blood count, basic metabolic panel, calcium, magnesium, and ASD levels (5 min). In some patients, diagnostic testing may include neuroimaging or lumbar puncture (0–60 min), additional laboratory testing (including liver function tests, coagulation studies, arterial blood gas, toxicology screen, and screening for inborn errors of metabolism), and C-EEG monitoring if the patient is not returning to baseline after clinical seizures cease (15–60 min) [15]. These recommendations are similar to those of the AAN practice parameter [29].

Among children with SE, neuroimaging abnormalities have been reported in 30% of children and appear to alter acute management in 24% [26]. If no etiology is identified by computerized tomography (CT), magnetic resonance imaging (MRI) may still identify lesions. Among 44 children who underwent both CT and MRI, 14 had normal head CT but an abnormal MRI [26].

Table 28.2 Recommended timeframes for benzodiazepine (BZD) and non-BZD anti-seizure drug (ASD) administration and ASD administration times in patients with refractory status epilepticus, and strategies that may reduce time to administration of anti-seizure medications

Type of anti-seizure drug (ASD)	Recommended timeframes of administration of ASDs, min	Median (P_{25}–P_{75}) times of administration in our series, min	Strategies that may reduce time to administration of ASDs
First benzodiazepine (BZD)	5–10	30 (6–70)	Seizure detection devices More widespread use of home BZDs by families More ready administration of BZDs by emergency services
First non-BZD ASD	10–20	69 (40–120)	Rapid escalation between categories of ASDs from BZDs to non-BZD ASDs to continuous infusions (or early polytherapy)
Second non-BZD ASD	20–30	120 (75–296)	Rapid escalation between categories of ASDs from BZDs to non-BZD ASDs to continuous infusions (or early polytherapy)
Continuous infusion	30–70	180 (120–645)	Consideration of continuous infusions early during hospital management Rapid escalation between categories of ASDs from BZDs to non-BZD AEDS to continuous infusions (or early polytherapy)

From Sánchez Fernández et al. [3], with permission

EEG monitoring may be indicated urgently if psychogenic SE is suspected [to avoid escalation of ASDs, with potential adverse effects] or if there is a concern that EEG-only seizures persist after termination of clinically evident seizures [30, 31]. A multi-center study of children who underwent C-EEG monitoring while in the pediatric ICU reported that 33% of 98 children who presented with CSE had subsequent electrographic seizures identified. Among those with seizures, electrographic SE occurred in 47% of subjects, and EEG-only seizures in 34% [32].

Central nervous system (CNS) infections are a common cause of acute symptomatic SE [26, 33, 34]. The clinical presentation of encephalitis and other CNS infections is highly variable depending on the pathogen involved and specific host factors. Fever and other clinical signs of infection may be absent in young children, individuals who are immunocompromised, or individuals who have received recent antibiotics. Lumbar puncture should be performed in all children with SE without a definite non-infectious cause. Guidelines from the Infectious Disease Society of America for adults recommend obtaining screening head imaging prior to lumbar puncture in patients who are immunocompromised, have a known space-occupying lesion or shunt, papilledema, or a focal neurologic deficit [35]. A lumbar puncture should also be obtained if an autoimmune etiology is suspected, as neuro-inflammatory processes will often yield cerebrospinal fluid pleocytosis, elevated cerebrospinal fluid protein, and intrathecal immunoglobulin synthesis (oligoclonal band profile, IgG index, and IgG synthesis rate). Rarer infectious, metabolic, autoimmune and paraneoplastic, and genetic etiologies may be considered in specific situations, or when other etiologies are not identified [20, 36].

Status Epilepticus Management—Early Benzodiazepine Management

Administration of appropriate ASDs should occur as the patient is medically stabilized and diagnostic studies are performed. Table 28.3 provides a summary of recommended medications and doses.

The NCS's guideline notes that benzodiazepines are the "emergent" medications of choice, with lorazepam for intravenous administration, diazepam for rectal administration, and midazolam for intramuscular, buccal, or intranasal administration. Repeat dosing may be provided in 5–10 min if seizures persist [15]. With regard to the initial benzodiazepine medications, the AES's guideline concluded that intravenous lorazepam and diazepam are efficacious at stopping seizures lasting at least 5 min (level A evidence) and that rectal diazepam, intramuscular midazolam, intranasal midazolam, and buccal midazolam are probably

Table 28.3 Dosing recommendations and common side effects for emergency (initial and second therapy phases) anti-seizure medications

	Medication	Dosing	Serious adverse effects	Other considerations
Initial therapy phase (emergency)	Lorazepam	IV: 0.1 mg/kg, up to 4 mg per dose. May repeat in 5–10 min	Hypotension, respiratory depression	Dilute 1:1 with saline IV contains propylene glycol
	Diazepam	IV: 0.15–0.2 mg/kg, up to 10 mg per dose. May repeat in 5–10 min Rectal: 0.2–0.5 mg/kg PR, up to 20 mg	Hypotension, respiratory depression	Short duration, active metabolite IV contains propylene glycol
	Midazolam	Adult IM: 0.2 mg/kg, up to 10 mg. Ped IM: 5 mg if 13–40 kg, 10 mg if > 40 kg. Intranasal: 0.2 mg/kg Buccal: 0.5 mg/kg	Hypotension, respiratory depression	Active metabolite, renal elimination, short duration For intranasal or buccal, use the IV formulation (5 mg/mL concentration)
Second therapy phase (urgent control therapy)	Phenytoin or Fosphenytoin	20 mg/kg phenytoin IV. May give additional 5–10 mg/kg. 20 mg PE/kg fosphenytoin IV. May give additional 5–10 PE/kg.	Hypotension, arrhythmias, 'purple glove syndrome' (phenytoin)	Phenytoin is only compatible in saline, and the IV contains propylene glycol Fosphenytoin is compatible in saline, dextrose, and lactated ringers solutions
	Levetiracetam	20–60 mg/kg IV	Aggression	Minimal drug interactions; not hepatically metabolized
	Phenobarbital	15–20 mg/kg IV May give an additional 5–10 mg/kg	Hypotension, respiratory depression	IV contains propylene glycol
	Valproic acid	20–40 mg/kg IV May give an additional 20 mg/kg	Hyperammonemia, pancreatitis, thrombocytopenia, hepatotoxicity	May be a preferred agent in patients with generalized epilepsy Avoid if possible with hepatic dysfunction, metabolic disease, <2 years old with unknown etiology, pancreatitis, or thrombocytopenia

Adapted from guidelines for status epilepticus management by the Neurocritical Care Society (Brophy et al. [15]) and the American Epilepsy Society (Glauser et al. [16])

effective at stopping seizures lasting at least 5 min (level B evidence). It indicates that there are three equivalent first-line options including intravenous lorazepam (0.1 mg/kg/dose; repeat once if needed), intravenous diazepam (0.15–0.2 mg/kg/dose; repeat once if needed), and intramuscular midazolam (10 mg for >40 kg; 5 mg for 13–40 kg; single dose) (level A evidence) [16]. A double-blind randomized trial of 273 children with CSE in the emergency department compared intravenous lorazepam (0.1 mg/kg) and diazepam (0.2 mg/kg). A half-dose of either medication could be administered if seizures persisted after 5 min. The primary outcome, SE cessation by 10 min without recurrence in 30 min, was not significantly different in the two groups (72% with diazepam; 73% with lorazepam). Subjects receiving lorazepam were more likely to be sedated (67% with lorazepam, 50% with diazepam) but there was no difference in the requirement for assisted ventilation (18% with lorazepam, 16% with diazepam). The study concluded that the data did not support preferential use of lorazepam over diazepam [37]. If intravenous access cannot be obtained, rectal, intramuscular, buccal, or intraosseous benzodiazepines can be administered. For buccal or nasal dosing of midazolam, the intravenous formulation of the drug is generally used in the United States.

Administration of benzodiazepines may result in respiratory depression and hypotension, so continued medical monitoring and stabilization is important. The AES's guideline noted that respiratory depression was the most common adverse event associated with ASD treatment (level A evidence) and that there was no difference in respiratory depression among midazolam, lorazepam, and diazepam by any administration route (level B evidence) [16]. In the clinical trial described above, assisted ventilation was required in 16% of the diazepam group and in 18% of the lorazepam group [37]. If the seizure does not terminate 5–10 min following initial benzodiazepine administration, a second benzodiazepine dose should be administered. Care should also be taken to assess whether pre-hospital administration of a benzodiazepine occurred, as excess benzodiazepine dosing increases the risk of respiratory suppression [4].

Status Epilepticus Management—Urgent Anti-Seizure Medication Management

SE will persist in about one-third to one-half of children receiving benzodiazepines [11, 18, 37], but there are few comparative data evaluating the ASD options available for this stage [38]. Common options include phenytoin (or fosphenytoin), levetiracetam, phenobarbital, and valproate. (see Table 28.1). The AES's guideline concluded that there was insufficient evidence to evaluate phenytoin or levetiracetam as second-line therapy (level U evidence) but that IV valproic acid has similar efficacy but better tolerability than IV phenobarbital (level B evidence) [16]. Optimal decisions may depend on patient characteristics, seizure characteristics, and also practical institutional factors, such as which drugs are most rapidly available as some need to be ordered and dispensed from a pharmacy.

Phenytoin is reported as the second-line medication by most respondents in surveys of pediatric emergency medicine physicians [39] and neurologists [40]. Phenytoin has demonstrated efficacy in pediatric SE management [41, 42], but its historical role as the most commonly used second-line medication is based on few data, and there are no studies showing it to be more effective than other options such as levetiracetam, phenobarbital, or valproate. A recent meta-analysis of drugs administered for benzodiazepine-refractory CSE found that phenytoin had lower efficacy (50%) than levetiracetam (69%), phenobarbital (74%), and valproate (76%) [38]. More information may be available in the near future as the NIH funded Established SE Treatment Trial (ESETT) will compare phenytoin, valproate, and levetiracetam for CSE in children and adults [43].

Both phenytoin and fosphenytoin are considered ASDs effective in focal seizures, but they may be ineffective or worsen SE in the generalized epilepsies. Phenytoin is prepared with propylene glycol and alcohol at a pH of 12, which may lead to cardiac arrhythmias, hypotension, and severe tissue injury if extravasation occurs (the "purple glove syndrome"). Fosphenytoin is a pro-drug of phenytoin, and it is dosed in 'phenytoin equivalents' (PE). Cardiac arrhythmias and hypotension may be less common with fosphenytoin because it is not prepared with propylene glycol, but they may still occur. There are numerous drug interactions due to strong hepatic induction and high protein binding, so free phenytoin levels may need to be checked [44]. Phenytoin causes little respiratory depression, particularly when compared to some other ASDs. The NCS's guideline classifies phenytoin and fosphenytoin as appropriate "emergent," "urgent", or "refractory" SE treatments, with an IV loading dose of 20 mg/kg (or for fosphenytoin, 20 "PE"/kg) [15]. The AES's guideline notes that there are insufficient data to compare phenytoin and fosphenytoin for efficacy (level U evidence) but that fosphenytoin is better tolerated than phenytoin (level B evidence). It recommends fosphenytoin (20 PE/mg) as an appropriate second therapy phase medication [16].

Valproic acid is a broad spectrum ASD often used for SE and refractory SE management. It has multiple mechanisms of action, including some independent of GABA receptors, making it potentially useful when benzodiazepines have been ineffective. In several meta-analyses, valproic acid was found to have the highest relative efficacy among typical second-line ASDs [38, 45–47]. Valproate may be administered rapidly IV and is considered appropriate "emergent," "urgent," or "refractory" SE treatment by the NCS's guideline, with a typical IV loading dose of 20–40 mg/kg [15]. The AES's guideline recommends valproic acid dosing of 40 mg/kg [16].

Several studies have evaluated valproate as an urgent medication for SE. One study compared it to phenobarbital in children; 60 children with CSE or acute prolonged seizures were assigned randomly to receive valproate (20 mg/kg) or phenobarbital (20 mg/kg). There was a non-significant trend ($p = 0.19$) toward greater seizure termination with valproate (in 27 of 30; 90%) than with phenobarbital (23 of 30; 77%). Clinically significant adverse effects (mostly lethargy) occurred significantly less often with valproate (24%) than with phenobarbital (74%). Seizure recurrence within 24 h was also lower with valproate than phenobarbital (15% vs. 52%) [48].

Several studies that included children have compared valproate to phenytoin. An open-label study of patients with SE (mostly adults, but some children) randomized patients to receive either valproate ($n = 35$, 30 mg/kg) or phenytoin ($n = 33$, 18 mg/kg) as a first-line medication. Valproate was more effective than phenytoin (66% vs. 42%) as first-line therapy, and after crossover to second-line therapy (79% vs. 25%). Adverse effects were not different between the two groups [49]. Another study of patients with SE refractory to benzodiazepines (mostly adults, but some children) compared valproate ($n = 50$) and phenytoin ($n = 50$), and found no difference in efficacy (84% vs. 88%, respectively). Among patients under 18 years of age, seizures terminated in 91% with valproate and in 75% with phenytoin [50]. In another study, patients older than 15 years with RSE received either valproate (mean loading dose, 1000 mg) or phenytoin (mean loading dose 743 mg). The two groups were the same in terms of seizure control, time to seizure control, hospitalization duration, and mortality [51].

Several studies have reported that valproic acid was effective in terminating RSE in 78–100% of children, without adverse effects [52–56]. A prospective study of 41 adults and children with refractory CSE included 5 patients younger than 5 years old treated with valproate, 30 mg/kg IV load, followed by an infusion at 6 mg/kg/h. Seizures

terminated in 88% within one hour, and no adverse effects were observed [54]. Another prospective open-label study of 40 children with RSE randomized subjects to receive IV valproate (30–40 mg/kg IV bolus) or a continuous diazepam infusion (10–80 mcg/kg/min). There was no difference in efficacy for seizure control (80% with valproate and 85% with diazepam infusion), but seizure control was more rapid with valproate (5 min with valproate, and 17 min with diazepam). No patient in the valproate group had adverse effects including need for ventilation or hypotension; 60% of those who received diazepam required ventilation, and 50% developed hypotension [55]. Several retrospective studies have also demonstrated that valproate often terminates RSE without major adverse effects [52, 53, 56].

Adverse events are infrequent with IV administration of valproic acid, but hypotension, thrombocytopenia, pancytopenia, platelet dysfunction, hypersensitivity reactions, pancreatitis, and hyperammonemia may occur. Valproic acid is a potent hepatic enzyme inhibitor and may increase levels of other medications. There is a Federal Drug Administration black box warning for hepatotoxicity, which is most common in children under 2 years of age receiving ASD polypharmacy and in those suspected of having mitochondrial or metabolic disorders. In the outpatient setting, valproic acid is estimated to cause hepatotoxicity in 1 in 500 children younger than 2 years of age and in children with metabolic disease; it must be used with caution in young children with SE of unclear etiology. A practice parameter on SE in children noted that data from 9 class III studies showed that an inborn error of metabolism was diagnosed in 4.2% of children with SE [29].

Levetiracetam is a broad spectrum ASD. Previously considered only for RSE, it has been used earlier in the course of SE due to its ease of dosing and lack of drug interactions. Levetiracetam has no hepatic metabolism, which may be beneficial in complex patients with liver dysfunction, or metabolic disorders. It has no drug interactions. In comparison to other ASDs available for IV administration, levetiracetam has a very low risk for sedation, cardio-respiratory depression, or coagulopathy. Since levetiracetam clearance is dependent on renal function, maintenance dosage reduction is required in patients with renal impairment. A growing number of observational [57] and retrospective case series and reports [58–67] indicate that levetiracetam may be safe and effective for treating both SE and acute repetitive seizures in children at IV loading doses of 20–60 mg/kg and without major adverse effects. The NCS's guideline considers levetiracetam to be an appropriate "emergent," "urgent," or "refractory" SE treatment option at 20–60 mg/kg [15]. The AES's guideline states that levetiracetam is an appropriate second therapy phase medication at 60 mg/kg [16]. A meta-analysis of drugs administered for benzodiazepine-refractory CSE found levetiracetam efficacious in 69% of subjects [38].

Phenobarbital is often considered a 3rd or 4th -line drug for pediatric SE. The NCS's guideline considers phenobarbital appropriate for treatment of emergent, urgent, or refractory phases of SE [15]. The typical IV loading dose is 20 mg/kg, with an additional 5–10 mg/kg if needed. A recent meta-analysis of drugs administered for benzodiazepine-refractory CSE found that phenobarbital was efficacious in 74% [38]. One study of 36 children with SE found that phenobarbital stopped seizures more quickly than a combination of diazepam and phenytoin; safety was similar with both [68]. Several reports have described the use of high-dose phenobarbital to control RSE and allow withdrawal of pharmacologic coma [69–71]. Phenobarbital may cause sedation, respiratory depression, and hypotension, so cardiovascular and respiratory monitoring is generally required. It is a hepatic enzyme inducer leading to drug interactions.

Refractory Status Epilepticus Management

RSE is characterized by seizures that persist despite treatment with adequate doses of initial ASDs. Definitions vary in seizure duration (with no time criteria, 30 min, 1 h, or 2 h), and by response or lack of response to different numbers (2 or 3) of ASDs. The NCS's guideline states that patients who continue to have either clinical or electrographic seizures after receiving adequate doses of an initial benzodiazepine followed by a second acceptable ASD have RSE [15]. Depending on the definitions and cohorts described, RSE occurs in about 10–40% of children with SE [12, 13, 41, 72].

In a subgroup of patients, RSE may last for weeks to months, despite treatment with multiple medications—which has been referred to as "malignant" RSE [73] or super-RSE [74, 75]. They are associated with infectious or inflammatory etiologies, younger age, previous good health, and high morbidity and mortality [73, 76, 77]. They have been referred to as de novo cryptogenic refractory multi-focal SE [77], new-onset RSE (NORSE) [76, 78, 79], and febrile infection-related epilepsy syndrome (FIRES) [80–82]; these terms may overlap in describing similar or identical entities [83].

The NCS's guideline indicates that when a benzodiazepine and "urgent" control medications are ineffective, clinicians may give another "urgent" control medication or proceed to initiate pharmacologic coma medications [15]. Additional urgent control ASDs may be reasonable if they have not been tried yet or if the patient needs to be transferred or stabilized prior to administration of continuous infusions. If an initial urgent control medication fails,

definitive seizure control should be initiated with continuous infusions. There should not be many trials of 'urgent control' medications before advancing to pharmacologic coma induction.

The management of pediatric RSE has been reviewed [20, 22, 84–87]. There is some variability among suggested approaches, as there are few data to guide evidence-based management [88], but all pathways administer either additional ASDs such as phenytoin, fosphenytoin, phenobarbital, valproate sodium, or levetiracetam, or they proceed to pharmacologic coma induction. The NCS's guideline recommends rapid advancement to pharmacologic coma induction rather than sequential trials of many "urgent control" ASDs [15]. Substantial delays have been described before administration of pharmacologic coma induction, indicating that attention to timing is important [3].

The medications used most often for induction of coma are midazolam, pentobarbital, and propofol. Midazolam use usually involves an initial loading dose of 0.1–0.2 mg/kg followed by an infusion at 0.05–2 mg/kg/h, titrated as needed to achieve clinical or electrographic seizure suppression or EEG burst–suppression. Pentobarbital dosing usually involves an initial loading dose of 5–10 mg/kg followed by an infusion at 0.5–5 mg/kg/h titrated similarly. If seizures persist with midazolam or pentobarbital, an escalating dose with additional boluses and increase in the infusion rate are needed to increase levels and terminate seizures rapidly. Increasing the infusion rate without additional bolus dosing will lead to a very slow increase in serum levels—inconsistent with the goal of rapid seizure termination. Anesthetics such as isoflurane are also effective in inducing a burst–suppression pattern and in terminating seizures but often cause vasopressor-requiring hypotension; seizures often recur upon weaning, and few data are available to guide use [89, 90]. Propofol may terminate seizures and induce burst–suppression rapidly [91], but it is rarely used in children due to its Federal Drug Administration black box warning of the propofol infusion syndrome [92].

Patients treated with continuous infusions or inhaled anesthetics require intensive monitoring due to concerns about numerous potential complications. First, continuous mechanical ventilation is usually needed for airway protection and to maintain appropriate oxygenation and ventilation. Second, central venous access and arterial access is important due to frequent laboratory sampling and a high likelihood of developing hypotension requiring vasopressor or inotropic support. Third, temperature regulation must be managed because high-dose sedatives and anesthetics can blunt the shivering response and endogenous thermoregulation. Fourth, assessment is important for development of lactic acidosis, anemia, thrombocytopenia, and end organ dysfunction such as acute liver or renal injury. Fifth, patients must be monitored for infections, with multiple risks for secondary infections due to indwelling catheters (central catheters, endotracheal tubes, Foley catheters) and immune suppressing medications (e.g., pentobarbital).

It remains unclear whether the EEG treatment goal of pharmacologic coma induction should be termination of seizures or a burst–suppression pattern on the EEG; either goal is considered appropriate by the NCS guideline [15]. It is also unclear how long the patient should be maintained in pharmacologic coma. The NCS guideline recommends 24–48 h of electrographic seizure control prior to a slow withdrawal of continuous infusion ASDs [15], consistent with a survey of experts in SE management [93]. A meta-analysis of midazolam for RSE found that much higher doses of midazolam were needed, with longer times to seizure control, in studies using EEG monitoring, compared to studies in which care was guided by clinical seizure identification, indicating that ongoing seizures may not be identified and targeted for treatment without EEG monitoring [88].

Electrographic or electro-clinical seizures frequently recur during weaning of pharmacologic coma medications [94–97], indicating that pharmacologic coma should be considered to provide a window to evaluate further for precipitant etiologies, initiate specific management when possible, and optimize the ASD regimen to provide seizure control as coma-inducing medications are weaned. Case reports and series have described several add-on medications, and other techniques have been reported useful in reducing seizure recurrence as pharmacologic coma is weaned, but there are no large studies to guide management. As summarized in several review papers, [20, 84, 87, 98] case series and case reports have described benefit with topiramate [71, 99–104], lacosamide [105–107], phenobarbital [68, 69, 108, 109], ketamine [110–114], pyridoxine [115–120], neurosteroids [121], lidocaine [122–124], the ketogenic diet [71, 83, 125–131], therapeutic hypothermia [132–136], immunomodulation [137, 138], epilepsy surgery [111, 139–149], vagus nerve stimulation [150], and electroconvulsive therapy [151–153].

Electrographic Seizures and Continuous EEG Monitoring

Seizures and SE are very common in critically ill children. Observational studies of interdisciplinary neurologic critical care teams at large pediatric institutions describe seizures and SE as the most commonly managed conditions, with EEG and EEG monitoring often performed [1, 2]. Studies of critically ill children undergoing clinically indicated C-EEG monitoring report that electrographic seizures occur in 10–50% of patients (Fig. 28.3); about one-third of critically ill children with electrographic seizures may be categorized as in electrographic SE (Fig. 28.4) [30, 31, 154–172]. The indications for C-EEG monitoring varied across these

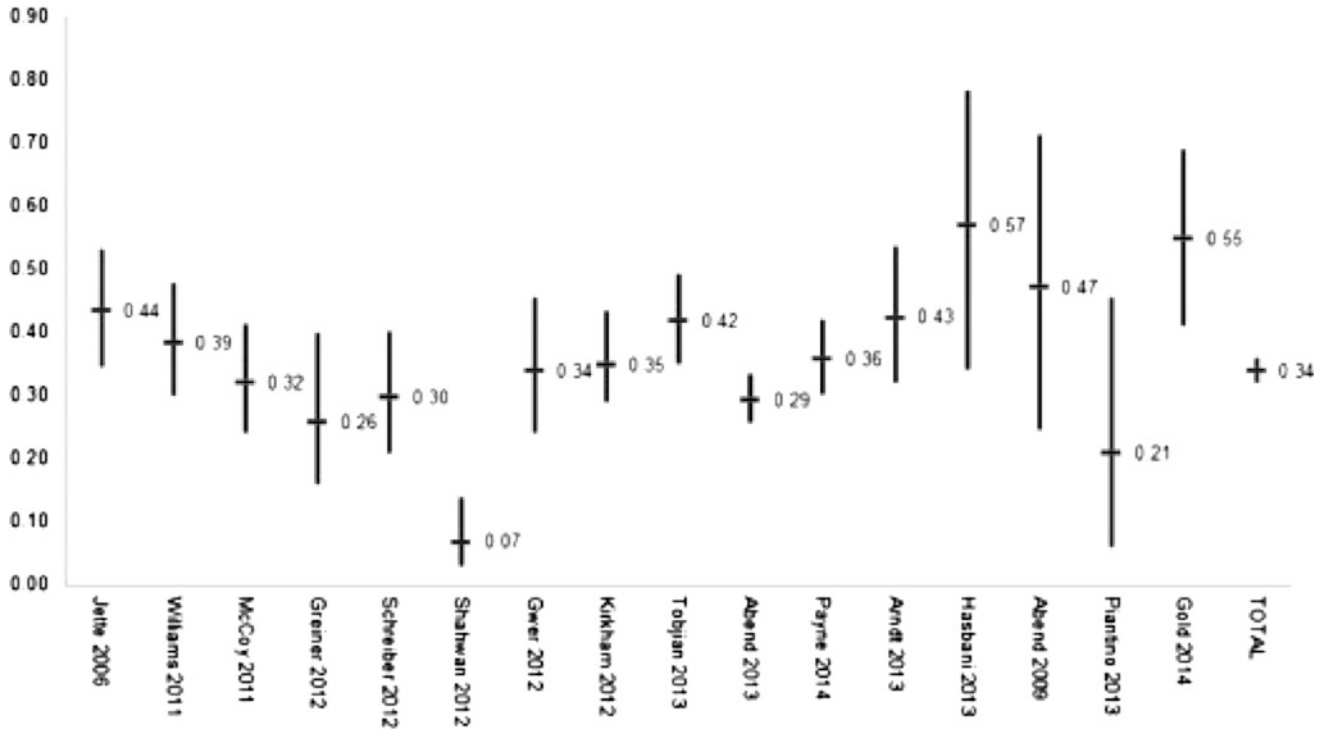

Fig. 28.3 Incidence of electrographic seizures in studies of continuous EEG monitoring in critically ill children. (From Abend [172], with permission.)

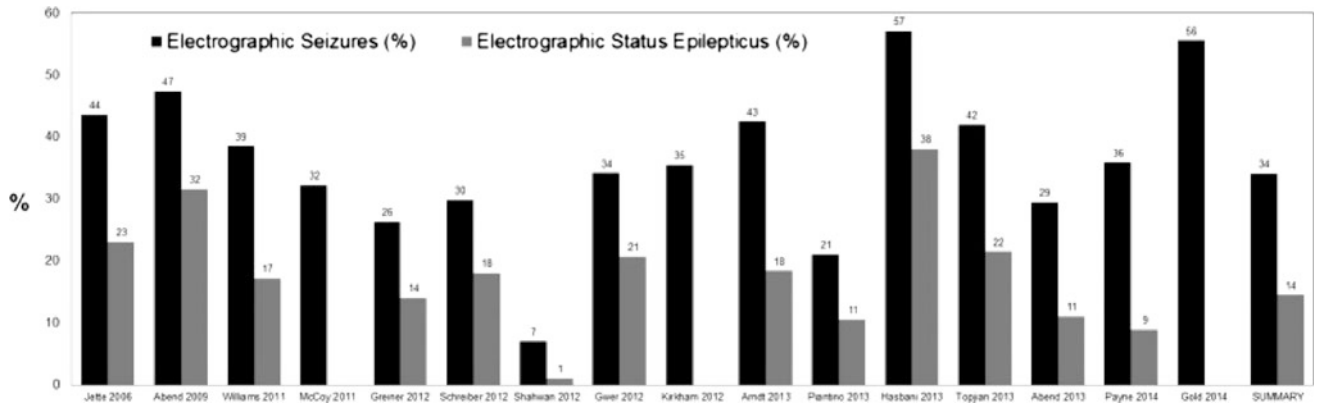

Fig. 28.4 Proportion of critically ill children who underwent clinically indicated continuous EEG monitoring with electrographic seizures (*black bars*) and electrographic status epilepticus (*grey bars*). (From Abend [172], with permission.)

studies. Some included only patients with known acute structural neurologic disorders (e.g., hypoxic-ischemic brain injury, encephalitis, or traumatic brain injury) while others included patients with encephalopathy due to broader and more heterogeneous diagnoses (e.g., both primary neurologic and primary medical conditions). Inclusion criteria variability may explain the broad range of reported electrographic seizure incidence—lower in studies with broader inclusion criteria. Additionally, many studies were small, as reflected in the wide 95% confidence intervals in Fig. 28.3. When individual subjects from these studies are analyzed together, the overall electrographic seizure incidence is 34%.

The largest epidemiologic study of C-EEG monitoring in pediatric ICUs was a retrospective study in which 11 tertiary care pediatric institutions each enrolled 50 consecutive subjects, thereby yielding 550 subjects. Electrographic seizures occurred in 30% of subjects. Among those with electrographic seizures, electrographic SE occurred in 33%, and EEG-only seizures in 35% [31]. These data are consistent with other single-center studies [30, 156, 159, 161–163,

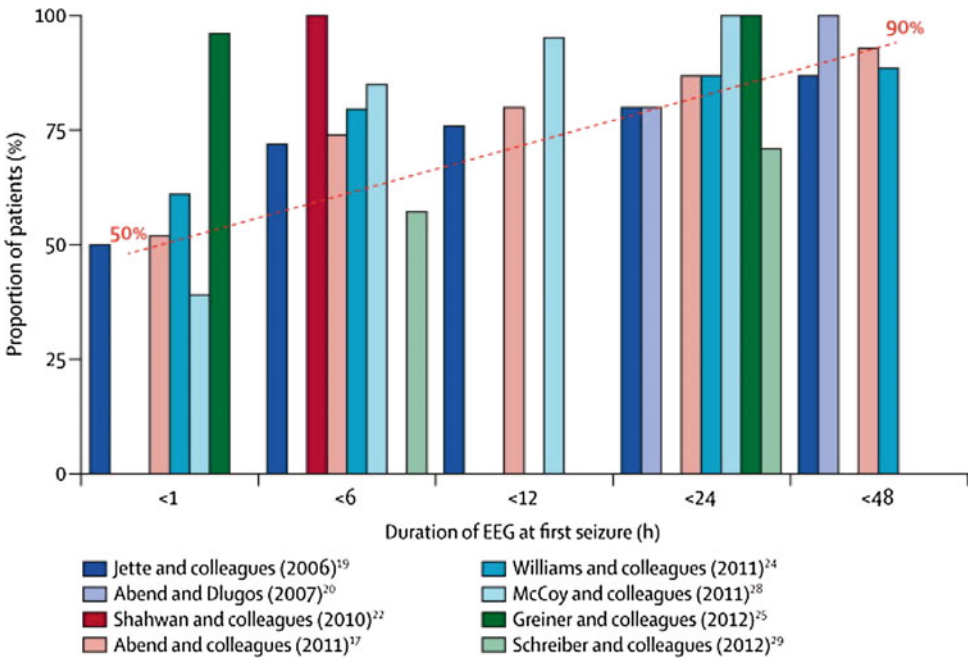

Fig. 28.5 Duration of EEG monitoring at onset of the first detected electrographic seizure in critically ill children. (From Abend et al. [154], with permission.)

165–168, 171]. Additionally, EEG-only seizures occurred in children who had not received paralyzing medications, recently or ever, during their ICU stay [30, 167], indicating the occurrence of an electromechanical uncoupling or dissociation, and not simply the masking of clinically evident seizures by paralytic medications.

C-EEG monitoring is resource-intense. Seemingly small utilization and workflow changes have substantial impacts on equipment and personnel needs [173, 174]. Identifying children at higher risk for having electrographic seizures may be beneficial in optimally directing limited C-EEG monitoring resources. There are several risk factors for electrographic seizures: 1. Younger age (infants as compared to older children) [30, 31, 161, 164, 168]; 2. Convulsive seizures [31, 162, 166] or convulsive SE [161] prior to the initiation of EEG monitoring; 3. Acute structural brain injury [160–162, 164–166, 168, 171]; and 4. Interictal epileptiform discharges [31, 161, 165, 166] or periodic epileptiform discharges [156]. These risk factors may have limited clinical utility in selecting patients to undergo C-EEG monitoring because the absolute difference in the proportion of children with and without electrographic seizures, depending on the risk factor, is often only 10–20%. Seizure prediction models combining multiple risk factors might allow better targeting of EEG monitoring in a given center [175].

Observational studies of critically ill children undergoing C-EEG note that about 50% of patients with electrographic seizures are identified within 1 h of C-EEG monitoring initiation, and 90% within 48 h of C-EEG monitoring initiation (Fig. 28.5) [30, 156, 157, 159, 161, 162, 166, 167]. Most studies calculated C-EEG duration from the onset of C-EEG rather than from the time of the acute brain insult. Patients generally underwent 1–3 days of C-EEG, and seizures may have occurred later, after C-EEG was discontinued. The NCS's Guideline for the Evaluation and Management of SE strongly recommends performing C-EEG monitoring for 48 h to identify electrographic SE in comatose children following an acute brain insult [15]. Similarly, the American Clinical Neurophysiology's (ACNS) Consensus Statement on Continuous EEG Monitoring in Critically Ill Children and Adults recommends performing C-EEG monitoring for at least 24 h in children at risk for electrographic seizures [176]. A survey of neurologists about EEG monitoring utilization noted that most perform 24–48 h of C-EEG monitoring when screening for electrographic seizures [177].

Several studies have identified an association between high electrographic seizure exposure and worse outcome, even after adjusting for potential confounders related to etiology and severity of acute encephalopathy, and critical

illness severity [31, 163, 169, 178, 179]. These studies indicate that there may be a dose-dependent or threshold effect of electrographic seizures on outcome. This threshold may vary based on age, brain injury etiology, and seizure characteristics such as the extent of brain involved and EEG features. Identifying and managing those seizures might mitigate injury. Further study is needed to develop optimal management strategies and assess their impact on outcomes.

A survey of C-EEG monitoring use in the ICUs of 61 large pediatric hospitals in the United States and Canada reported about a 30% increase in the median number of patients who underwent C-EEG monitoring per month from 2010 to 2011. Indications for C-EEG monitoring included determining whether events of unclear nature were seizures in 100% of centers, and identifying electrographic seizures in patients considered "at-risk" for seizures (e.g., altered mental status following a convulsion, or a known acute brain injury, or of unknown etiology) in about 90% of centers. About 30–50% of centers reported using C-EEG monitoring as part of the standard management for specific acute encephalopathy etiologies, e.g., following resuscitation from cardiac arrest or with severe traumatic brain injury [180].

Two national associations have provided guidelines or consensus statements regarding EEG monitoring in critically ill children. The NCS's Guidelines for the Evaluation and Management of SE recommends 48 h of C-EEG monitoring to identify electrographic seizures in at-risk patients, including patients with persisting altered mental status for more than 10 min after convulsive seizures or SE; and encephalopathic children after resuscitation from cardiac arrest, with traumatic brain injury, with intracranial hemorrhage, or with unexplained encephalopathy. If SE (including electrographic SE) occurs, the guideline recommends that management should continue until both clinical and electrographic seizures are halted [15]. The ACNS's Consensus Statement on Continuous EEG Monitoring in Critically Ill Children and Adults recommends C-EEG monitoring for 24–48 h in children at risk for seizures. EEG monitoring indications include: (1) Recent convulsive seizures or convulsive SE with altered mental status, (2) Cardiac arrest resuscitation or with other forms of hypoxic-ischemic encephalopathy, (3) Stroke (intracerebral hemorrhage, ischemic stroke, and subarachnoid hemorrhage), (4) Encephalitis, and (5) Altered mental status with related medical conditions. The consensus statement provides additional detailed recommendations regarding personnel, technical specifications, and overall workflow [176]—which may need to be individualized based on resources and practice patterns at each institution. The Children's Hospital of Philadelphia's Intensive Care EEG Monitoring pathway is available online [181].

Given the rapid expansion of C-EEG monitoring and a limited number of electroencephalographers and EEG technologists, more efficient methods of EEG screening are needed. Since electroencephalographers and EEG technologists generally review C-EEG only intermittently, delays may occur between electrographic seizure onset and management initiation [24, 177, 180]. Quantitative EEG (Q-EEG) techniques may improve C-EEG review efficiency by electroencephalographers and allow more involvement by bedside clinicians, which could improve seizure identification. Q-EEG techniques separate the complex EEG signal into components (such as amplitude and frequency) and compress time, thereby displaying several hours of EEG data on a single image that may be interpreted more easily and rapidly than conventional EEG [182]. The most commonly utilized Q-EEG techniques are amplitude-integrated EEG (aEEG) which is based on amplitude and color density spectral array (CDSA) which is based on both amplitude and frequency. Seizures often involve increases in waveform amplitude and frequency, so they may be identified using these techniques (Fig. 28.6).

Several studies have evaluated the use of Q-EEG techniques by electroencephalographers and nonexpert users [183–186]. Sensitivity is good but imperfect. Specificity is also good, but imperfect; so some non-seizure events might be categorized as seizures, potentially leading to overtreatment and exposure to unnecessary ASDs. Seizures that are focal, lower in amplitude or frequency, or brief, are not identified as well using Q-EEG techniques. With further development, synergistic approaches may include a bedside caregiver using a Q-EEG display for seizure screening, with subsequent confirmation of the seizure diagnosis by raw EEG review by an electroencephalographer, thus making use of the efficiency and bedside availability of Q-EEG methods, with the accuracy of conventional EEG interpretation.

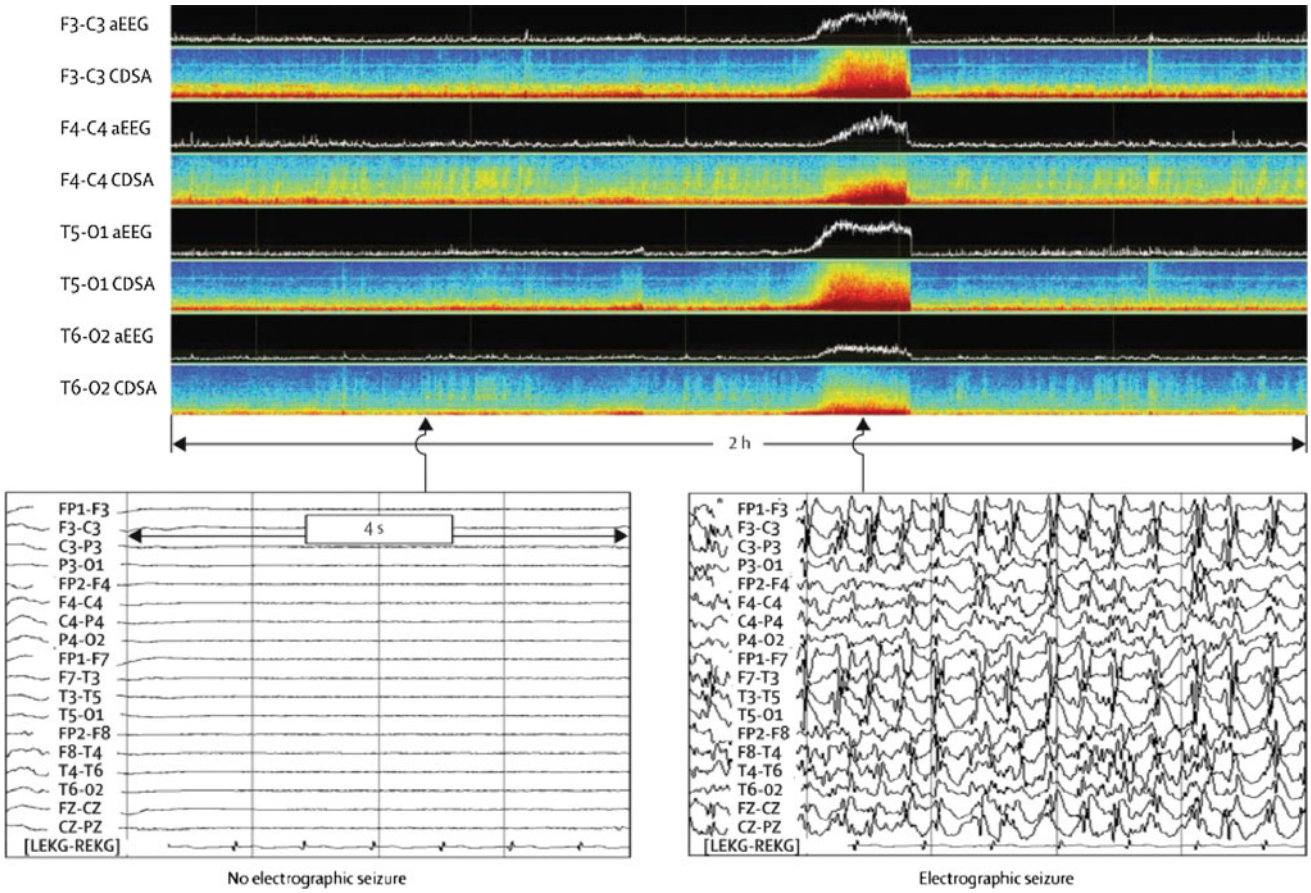

Fig. 28.6 Amplitude integrated EEG (aEEG) and color density spectral array (CDSA) image showing an electrographic seizure in a critically ill child. The electrographic seizures are characterized by increases in amplitude (*displayed as increases on the* y-*axis*) on the aEEG and CDSA tracings, and also by an increase in power (*displayed as warmer colors*) on the CDSA tracing. (From Abend et al. [154] with permission.)

Conclusions

Status epilepticus is common in critically ill children. Rapid management is needed to avoid systemic complications, identify and manage precipitating conditions, and terminate seizures. A predetermined management plan that is optimized for an individual institution and emphasizes rapid progression through appropriately dosed ASDs may help streamline management. Children with or without prior convulsive seizures may have electrographic SE, which can often be identified only by using C-EEG monitoring.

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Designing New Studies in Status Epilepticus

29

Jong Woo Lee and Cecil D. Hahn

Introduction

Our knowledge of status epilepticus (SE) is at a crossroads. Careful observational studies have taught us much about the natural history of SE. Routine use of continuous electroencephalographic (CEEG) monitoring has shown us that subclinical seizures account for a majority of the seizure burden in SE, and that a variety of periodic and rhythmic EEG patterns exist on a continuum with electrographic seizures. Advances in quantitative electroencephalographic (QEEG) trending techniques have permitted more efficient visualization of prolonged EEG recordings. Increased access to secure Internet-based data collection and sharing has made multicenter collaborative studies far more feasible than in the past. Multimodality intracranial monitoring technologies have illuminated the metabolic and functional changes that accompany seizures. Leveraging all of these advances in knowledge and technology opens a wide array of possibilities in designing new studies in SE.

In this chapter, we illustrate how recent advances in our understanding of SE, advances in clinical trial methodology, and advances in technology can be harnessed to improve the design of future studies of SE. Clinical trials remain the cornerstone of what influences management practices and outcomes. By their nature, well-performed clinical trials in SE are difficult to plan and execute, and exact a marked cost, both in effort and financially. Novel clinical trial designs need to be incorporated into future studies to optimize their power, accelerate their conduct, and reduce their cost. Methodological improvements in the assessment of seizure burden are needed. It has become clear that the clinical assessment of seizures is inaccurate, and that CEEG monitoring is required to quantify seizure burden accurately in future studies of SE. Furthermore, the identification and treatment of the underlying etiology of SE will permit more individualized therapy, improving the power of clinical trials. Finally, we must keep in mind that SE poses a significant global health burden, and that unique strategies will be required to optimize care in resource-poor countries.

Tribulations in Status Epilepticus Clinical Trial Design

Historically, SE treatment trials have focused primarily on determining the optimal sequence of anti-seizure drugs (ASDs) that can be used to abort seizures. This approach continues with the Established Status Epilepticus Treatment Trial (ESETT) [1]. Recently, however, doubt has been cast on whether rigorous adherence to treatment guidelines actually improves outcomes [2]. Far simpler variations in institutional practices, such as ensuring adequate dosing of initial benzodiazepine therapy, have been shown to have a substantial influence on outcome [3, 4]. Furthermore, the power of conventional clinical trials is limited by the fact that SE has a large variety of underlying etiologies. Future clinical trials may be more likely to succeed if they enroll populations with homogeneous SE etiologies, such as brain tumors, subdural hemorrhages, prior epilepsy, hypoxic brain injury, or traumatic brain injury. Alternatively, clinical trials could combine ASD treatment with protocolized attempts to identify the underlying cause and initiate etiology-specific therapies rapidly.

It has also become apparent recently that safety of the treatment of SE may play an important role in outcome. Fatal iatrogenic complications such as bowel ischemia or multiple organ failure are not uncommon in patients undergoing prolonged coma treatment [5, 6]. Several studies have shown that mortality and morbidity are markedly

J.W. Lee
Department of Neurology, Brigham and Women's Hospital, 75 Francis Street, Boston, MA 02115, USA
e-mail: jlee38@partners.org

C.D. Hahn (✉)
Division of Neurology, The Hospital for Sick Children, 555 University Avenue, Toronto, ON M5G 1X8, Canada
e-mail: cecil.hahn@sickkids.ca

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increased in patients undergoing coma-inducing treatment with anesthetic medications [7, 8]. Because these studies were observational in nature, however, this association may simply be due to a selection bias of the most critically ill patients receiving these treatments.

At this time, there is little agreement regarding the indication for coma induction, depth of coma (to either burst suppression or seizure suppression), medication sequence, or duration of coma [9]. Therefore, a carefully designed clinical trial to answer the true utility of EEG suppression is needed. The time is opportune for such a trial to be performed, given recent advances in CEEG monitoring technology, including improved data visualization with QEEG tools [10, 11] and the existence of a network of institutions with common experience gained in performing the neurophysiology-guided Treatment of Recurrent Electrographic Nonconvulsive Seizures (TRENdS) trial [12].

Innovation in Clinical Trial Design

Several recent innovations in clinical trial design can be harnessed to generate better evidence for more effective SE treatments more efficiently.

Adaptive Trial Design

The implementation of modern clinical trial designs should be considered in all future trials in SE. With increasing computing power, Bayesian adaptive trials have now become feasible. In traditional trial designs, all key parameters are pre-defined prior to the execution of the trial. Adaptive clinical trials take advantage of accumulating information during the trial, allowing for adjustments to treatment parameters and trial termination criteria during the trial itself. Adjustments include preferential allocation of patients to a better performing arm of the study, alterations in treatment dose, and alterations in inclusion and exclusion criteria to enrich the study population. Such designs have the potential to provide greater power and reduce the number of subjects required, thereby reducing study cost and reducing the likelihood of drawing incorrect conclusions [13]. SE studies are particularly well suited for adaptive designs because of the possibility of large morbidity, a rapidly available biomarker in EEG, and the expected scarcity of patients. Examples of recent trials that have used adaptive designs include the Neonatal seizure treatment with Medication Off-patent (NEMO) trial of bumetanide for seizures in newborns with hypoxic ischemic encephalopathy [14]; a randomized trial of seizure prophylaxis in patients with brain tumors [15]; and a randomized trial of clonazepam versus clonazepam plus concurrent levetiracetam for out-of-hospital SE (SAMUKeppra) [16]. A Bayesian adaptive design is also implemented for the ESETT based on simulations that have indicated a substantial potential benefit of this approach [17].

Improving the Measurement of Seizure Burden

A key design consideration for studies of SE is how seizures are measured. It is widely accepted that the most accurate ascertainment of seizures is by EEG, where seizures are recognized as rhythmic EEG patterns, often with a spike-and-wave component, that evolve in frequency, amplitude, and morphology, with a clear onset and offset [18]. Studies have demonstrated that the inter-rater agreement for assessing EEG seizures is high [19, 20], justifying the quantification of EEG seizures as a research measure.

Nevertheless, it has also become clear that not all seizures are easily distinguished from other rhythmic and periodic EEG patterns (e.g., periodic discharges or rhythmic delta activity) that are encountered frequently in critically ill patients [18]. Furthermore, some types of periodic discharges have been independently associated with a greater risk for acute seizures and worse outcome [21–23], raising the question of whether periodic discharges alone warrant initiation of ASD therapy. Therefore, any study of acute repetitive seizures or SE that uses EEG to ascertain seizures needs to consider how to address subjects who manifest EEG patterns on this ictal–interictal continuum.

The alternative to EEG assessment of seizures is the clinical assessment by bedside caregivers. Clinical assessments are easier to implement in a research study because they do not require mobilization of EEG monitoring resources, the availability of which varies greatly among centers, particularly after hours. The clinical assessment of seizures, however, lacks precision. Clinical assessments will fail to recognize nonconvulsive (a.k.a. 'subclinical,' or EEG-only) seizures, which frequently follow convulsive seizures and represent the majority of seizures in critically ill patients. Furthermore, various non-epileptic events (e.g., cardiac syncope or psychogenic non-epileptic events) may be misclassified as seizures. Therefore, whenever feasible, the clinical assessment of seizures should be complemented by EEG.

The quantification of seizure burden is central to establishing a treatment threshold and then to assessing the response to treatment. A variety of approaches has been used to characterize seizure burden. Seizure count is simply the number of seizures, usually expressed per unit of time. Seizure duration is the electrographic duration of a seizure from onset to offset. Seizure count and duration may be further refined by including only seizures that have a certain minimum duration (e.g., 5 min). Seizure extent refers to the anatomical extent of seizure involvement, which can either be categorized (e.g., focal, multifocal, hemispheric, bilateral,

generalized) or quantified (e.g., number or involved channels in a given EEG montage).

Total seizure burden reflects the cumulative burden of seizures over the entire monitoring period, which may, of course, vary in intensity. To account for monitoring periods of varying duration, the total seizure burden can be divided by the duration of monitoring to compute the seizure burden proportion. Alternatively, seizure burden can be calculated for a series of fixed time periods (e.g., hourly), or by using a sliding time window of fixed duration (e.g., 1 h). The resulting values can then be reported as maximum, minimum, mean, or median. The maximum hourly seizure burden represents the maximum proportion of any given hour that is spent seizing, which is a reflection of the peak intensity of seizures during the monitoring period.

Reporting seizure burden over a series of fixed time periods or by using a sliding time window has the advantage that it becomes a dynamic measure that can be calculated on an ongoing basis in real time and can therefore be used to guide therapy, whereas total seizure burden would not be known until the end of the monitoring period. It remains to be determined which of these seizure burden measures correlates best with outcomes. All of the above metrics can be refined further by including only seizures with a certain minimum duration (e.g., ≥ 1 min) or a certain anatomical extent (e.g., categorized as hemispheric, or involving 3 or more EEG channels).

Defining Seizure Treatment Thresholds and Response Criteria

Beyond the choice of ASD types, doses, and routes of administration, the choice of seizure treatment thresholds and response criteria are crucial to the effective design of treatment trials for recurrent seizures and SE. The seizure treatment threshold defines when a given therapy should be initiated or escalated, and should specify a precise burden of seizures (or periodic discharges) defined in terms of duration, frequency, and anatomical extent. The response criterion defines when a given therapy is deemed to have been successful. The simplest response criterion is "freedom from further seizures for a given duration." In trials involving successive escalation of ASD therapy, the response criterion may be defined as maintaining a seizure burden that is lower than the next treatment threshold for a given duration. The time point at which the response criterion is to be assessed must be defined clearly, and should take into account the pharmacokinetic and pharmacodynamic properties of the ASD therapy, as well as the frequency of EEG interpretation. In addition, investigators should take into account "regression toward the mean" in the seizure burden when assessing response to treatment, a phenomenon which can only be fully addressed through treatment randomization. Table 29.1 illustrates a hypothetical protocol that employs escalating treatment thresholds.

Accounting for the Influence of Seizure Etiology

One of the greatest challenges in designing effective interventional studies for acute repetitive seizures and SE is accounting properly for the contribution of the underlying seizure etiology. Etiology has long been recognized as an important determinant of both the refractoriness of acute seizures to treatment and long-term outcome. Therefore, studies must be carefully designed to take underlying seizure etiology into account. The seizure etiology may directly worsen outcome through a direct brain injury that is independent of seizures (e.g., stroke, hypoxic ischemic brain injury, or traumatic brain injury), or etiology may modify the deleterious effects of seizures, or both. For example, in the context of traumatic brain injury, seizures have been shown to be associated with a state of local "metabolic crisis" [24]. Perhaps the simplest solution to this problem is to limit study enrolment to patients with only a single etiology. This strategy, however, poses other challenges: the etiology is not always known at the time of seizure onset and study enrolment, and restrictive enrolment criteria can severely reduce recruitment rates. Furthermore, even when studying a single etiology, variations in etiology-specific injury severity must still be measured (e.g., neuroimaging measures of infarct volume or traumatic brain injury severity) and factored into analyses of the relationship amongst seizure burden, treatment, and outcomes. Studies that do include patients with multiple seizure etiologies must either stratify the analysis of outcomes by the underlying etiology or, if pooling the analysis of multiple etiologies, consider the possible effect modification of etiology on seizure burden (Fig. 29.1) [25]. In certain cases, the influence of etiology on outcome will likely overwhelm the effects of seizures (e.g., anoxic brain injury) or may mitigate their effects (e.g., epilepsy of presumed genetic origin). Therefore, careful consideration of the influence of seizure etiology is crucial to successful study design and execution.

From Clinical Trials to Individualized Therapy

Although much attention has been paid to shortening the time to seizure cessation by optimizing the use of conventional ASDs and coma-inducing drugs, the most important factor determining outcome remains the underlying etiology [26]. Rapid identification and treatment of underlying etiologies that are amenable to intervention would likely optimize outcome further.

Table 29.1 Example of protocol with escalating treatment thresholds coupled to escalating treatment intensity

Stage	Treatment threshold	Treatment	Response criterion
Prophylaxis	Periodic discharges lasting ≥ 1 min	Start maintenance therapy with ASD #1	No progression to seizures
1st line therapy	Single seizure lasting ≥ 1 min (with any anatomical extent)	Loading dose of ASD #1, increase maintenance dose of ASD #1	Seizure burden remains below next treatment threshold for ≥ 24 h
2nd line therapy	Single seizure lasting ≥ 2 min, or 3 or more seizures within 1 h each lasting ≥ 1 min (anatomical extent ≥ 2 channels)	Loading dose of ASD #2, start maintenance therapy of ASD #2	Seizure burden remains below next treatment threshold for ≥ 24 h
3rd line therapy initiation	Single seizure lasting ≥ 2 min, or 3 or more seizures within 1 h each lasting ≥ 1 min (anatomical extent ≥ 2 channels)	Start infusion of anesthetic drug #1	Seizure burden remains below next treatment threshold for ≥ 24 h
3rd line therapy escalation	Single seizure lasting ≥ 2 min, or 3 or more seizures within 30 min each lasting ≥ 1 min (anatomical extent ≥ 2 channels)	Increase infusion rate of anesthetic drug #1, up to a pre-defined maximum	Seizure burden remains below next treatment threshold for ≥ 24 h
4th line therapy initiation	Single seizure lasting ≥ 5 min, or 3 or more seizures within 30 min each lasting ≥ 2 min (anatomical extent ≥ 2 channels)	Start infusion of anesthetic drug #2	Seizure burden remains below next treatment threshold for ≥ 24 h
4th line therapy escalation	Single seizure lasting ≥ 5 min, or 3 or more seizures within 30 min each lasting ≥ 2 min (anatomical extent ≥ 2 channels)	Increase infusion rate of anesthetic drug #2, up to a pre-defined maximum	Seizure burden remains below next treatment threshold for ≥ 24 h

Note that the seizure burden used to define treatment thresholds is expressed in terms of seizure duration and anatomical extent
ASD = anti-seizure drug

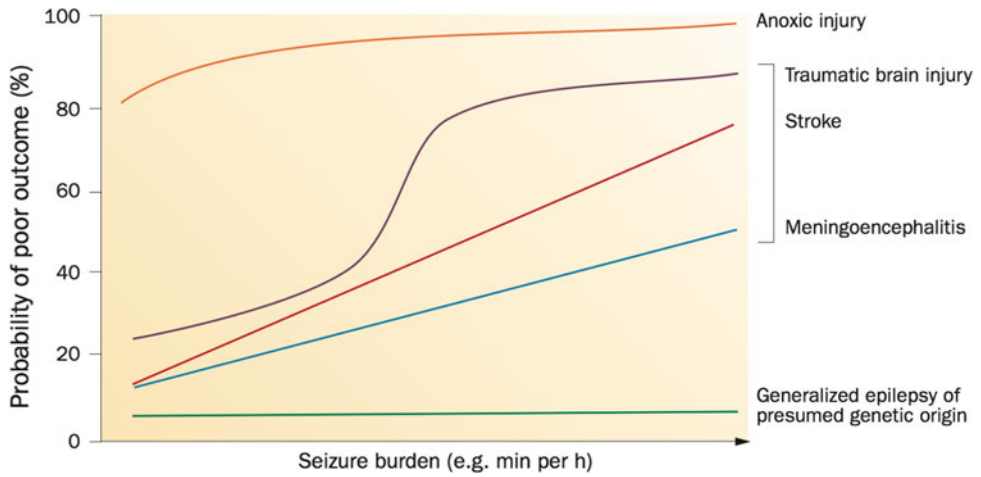

Fig. 29.1 Schematic illustration of potential relationships between seizure burden and outcome. The potential deleterious effects of seizures in the context of acute brain injury are likely to depend on the underlying etiology. The probability of poor outcome may increase linearly or exponentially with increasing seizure burden, or a threshold may exist, above which seizures are harmful. (From Hahn and Jette [25], with permission)

While the search for an underlying etiology is often straightforward in patients with known cerebral structural abnormalities such as a brain tumor, stroke, or traumatic brain injury, when no such known condition is present the search may be more vexing. Nevertheless, persistence in the search for an etiology can reap significant rewards. In a study of patients with new onset refractory status epilepticus (NORSE) in whom an underlying etiology was not identified within 48 h of admission, subsequent investigations identified an autoimmune etiology in 19% and a paraneoplastic etiology in 18% [27]. Still, in more than 50% of these patients no etiology was found despite extensive investigations, indicating substantial room for improvement in current diagnostic approaches [27]. Identifying the underlying etiology of patients with cryptogenic SE will be of paramount importance in enabling etiology-specific therapies that have the potential to improve outcome.

The search for the underlying etiology for cryptogenic SE is often difficult, largely due to the fact that a large number of illnesses may manifest as SE, possibly via a common terminal mechanism. Cases of SE that remain cryptogenic after initial investigation are likely due to a variety of underlying causes, rather than to some common as-yet unknown cause. Therefore, strategies to identify etiologies that affect only a small number of patients or even unique patients should be implemented. Such rare causes of SE include mitochondrial disease and other inborn errors of metabolism [28, 29].

The identification of autoimmune diseases as an important cause of cryptogenic SE (and epilepsy in general) is an example of the remarkable successes that can be achieved by etiology-specific diagnosis and therapy. These findings serve as a model for identifying other SE etiologies. The recognition that extreme delta brushes on EEGs are found in patients with anti-NMDA receptor encephalitis has been instrumental in the early identification of these patients, allowing rapid initiation of immunomodulatory therapy even before the specific autoantibodies are confirmed [30]. The discovery of extreme delta brushes was made possible by a multicenter collaborative effort, demonstrating the importance that collaborative research has for the characterization of cryptogenic SE etiologies.

Although an autoimmune etiology may be suspected quite early, it can take months or even years to identify specific causative autoantibodies [31]. To address this challenge, we propose the establishment of a centralized repository for banking of serum from patients with cryptogenic SE, with the goal of facilitating substantial advances in diagnosis. In addition to serum samples, this centralized repository would include detailed clinical information, imaging data, EEG tracings, and cerebrospinal fluid samples when available. In addition, genotyping and metabolomics analyses could be performed centrally or through a bio-specimen core. A careful curation process would need to be put in place to assure the integrity of the collected data.

The power of such a repository would be increased markedly by making it publicly available through an easy to navigate web-based interface. For example, the Cancer Genome Atlas is a repository of carefully curated datasets that, due to its publicly available nature, has benefitted nearly every aspect of cancer research by identifying 10 million new mutations that represent key drivers for a number of cancers, leading to more effective targeted therapies. The Epilepsy Phenome/Genome Project (EPGP) is another model of a multi-institutional study in which detailed phenotypic characteristics and DNA samples were bio-banked. Key to the success of both of these bio-banks is their core-based organizational structure, in which a number of institutions each serves distinct administrative or scientific functions [32].

The challenges of creating and maintaining such a repository are formidable. Refractory SE remains a relatively rare entity, so data will have to be collected by a large number of sites. Multifactorial data, often large and complex in nature due to high throughput genomic methods, continuously recorded physiologic and electrographic data, and high-resolution multimodal imaging technologies, must be collected and integrated in a standardized manner, addressing security and patient confidentiality [33, 34]. Such a repository would require a substantial investment in infrastructure. Technologic advances may present opportunities for research studies performed using such a dataset. As high-fidelity DNA and RNA sequencing is becoming more standardized and more widely available, novel methods of sharing such data are being developed [35]. High-quality institutional bio-banks may also facilitate this process and reduce costs [34]. Finally, it is increasingly recognized that strong financial incentives to identify, enroll, and complete study procedures are an essential driver for study completion [32]. Poorly funded registries that depend on investigator volunteerism are less likely to produce meaningful advances.

Recently, it has become clear that large collaborative efforts can drive significant advances in the field of epilepsy [36]. Although multicenter research entails certain logistical and technological challenges, maintaining clear lines of communication is often the biggest challenge. Therefore, the most important piece of infrastructure is the establishment of methods of clear, transparent communication that is inclusive of a large number of disparate centers, so that repository and study goals can be established efficiently. With this goal in mind, the Critical Care EEG Monitoring Research Consortium (CCEMRC) developed a common terminology to describe EEG patterns in patients undergoing CEEG monitoring [37]. Although initially developed for research purposes, this has evolved into the American Clinical

Neurophysiology Society's standard critical care EEG terminology. It is widely used now in clinical practice and was recently incorporated into a multicenter research and clinical database [38]. In addition, several multicenter observational SE registries have been established, underscoring the importance of large collaborative efforts [39, 40].

Status Epilepticus in Developing Countries

It is estimated that over 85% of the global burden of epilepsy is borne by resource-poor countries, defined as low- or middle-low-income countries [41]. Although the global burden of epilepsy and SE is difficult to estimate accurately, the incidence and prevalence of epilepsy in developing countries is likely to be markedly higher than in the developed world [42]. Mortality in convulsive status epilepticus is higher across all age groups in resource-poor regions [43, 44]. Furthermore, sequelae from SE such as focal neurologic deficits and cognitive deficits are more frequent in developing regions [42].

Modern operational definitions of SE may not be practically applicable in resource-poor countries due to the frequent lack of documentation regarding seizure duration [41]. Most existing studies have been performed on convulsive SE because the assessment of nonconvulsive SE (NCSE) is difficult in these regions. The incidence of NCSE in developing countries is similar to that in developed countries [45], but the distribution of underlying etiologies is different: febrile SE, infectious etiologies, and traumatic brain injuries are more common in developing countries. Among patients admitted with seizure-related illnesses in those countries, a greater proportion has SE [46].

The epilepsy treatment gap between developing and developed regions remains substantial [47]. Causes of the epilepsy treatment gap include a scarcity of skilled healthcare practitioners, inability to pay for treatment, unavailability of drugs, local cultural beliefs, use of traditional medicines, and distance from healthcare facilities [41, 48]. A concerted effort to address this gap has been made through the World Health Organization and the International League Against Epilepsy (ILAE), specifically to reduce the physical and social burden of epilepsy, to train and educate healthcare professionals, to dispel stigma, to identify and assess interventions that may lead to epilepsy prevention, and to develop a worldwide model for integration into local health systems [49]. Whether these initiatives have actually reduced treatment gaps in SE remains to be demonstrated.

The treatment gap in SE shares many of these challenges, but it differs in other respects. Several common challenges include the unavailability of medications and the distances from health care facilities. Also, because SE may be more readily recognized as a neurologic emergency, it may not share the same social and cultural barriers (such as stigma based on cognitive or psychiatric dysfunction), though it likely shares others (such as fear that seizures are contagious [41]). One significant gap is the inability to pay for comprehensive diagnosis and treatment. The nature of seizures in patients with acute non-traumatic coma mirrors that in developed regions in that most seizures in these patients are nonconvulsive, detectable only through EEG, and are independently associated with poor outcome [50]. Yet, the cost of EEG equipment and, particularly, the trained personnel required to perform and interpret the EEG remain prohibitive in many resource-poor countries.

Although continued advances in the basic healthcare infrastructure of resource-poor countries will help to reduce the treatment gap for SE gradually, there are opportunities to narrow this gap more quickly by harnessing recent advances in technology. Producing ultra-affordable hardware has been demonstrated through projects such as the Raspberry Pi, where a full-functioning, reasonably powered computer could be produced for $5–25 [51]. A similar approach could be taken to design and manufacture an inexpensive basic EEG acquisition system that could be operated with minimal training, to reduce the cost of EEG substantially. Multiple studies have demonstrated the relatively good performance of reduced channel montages in detecting seizures and SE [52–54]. Furthermore, the growth of the telecommunications industry in the developing world, particularly in mobile broadband, has been remarkably rapid, with internet penetration now surpassing 35% [55]. Access to mobile broadband could be harnessed for education and training and creates the possibility for remote EEG review, increasing access to neurophysiologist expertise.

Conclusion

SE remains a significant global health problem that imposes a significant burden on societies worldwide. Current treatment options often fail to control seizures in a timely manner and expose patients to potentially harmful side effects. Fortunately, the above strategies hold great promise for designing new studies that will allow us to improve SE treatment further in both resource-rich and resource-poor countries.

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