Seizures in Critical Care

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Seizures in Critical Care

A Guide to Diagnosis and Therapeutics

Second Edition

Edited by

Panayiotis Varelas, MD

Henry Ford Hospital
Detroit, MI
USA

Humana Press

Editor
Panayiotis Varelas
Henry Ford Hospital
Detroit, MI
USA

ISBN 978-1-60327-531-6 e-ISBN 978-1-60327-532-3
DOI 10.1007/978-1-60327-532-3
Springer New York Dordrecht Heidelberg London

Library of Congress Control Number: 2009933998

Printed on acid-free paper

Springer is part of Springer Science+Business Media (www.springer.com)

Preface to the Second Edition

Seizures in Critical Care: A Guide to Diagnosis and Therapeutics was published in the end of 2004. Based on the communication that my co-authors and I had with various health care providers, it was received very positively and was widely used as a reference book in many Intensive Care Units. It also received reviews in international journals and even from the World Federation of Neurology.

This positive attitude towards the book, and the fact that 5 years have passed since, made us entertain the idea of a second edition. My hope, as I have noted in the Preface of the first edition, was that " … it should constitute a testimony of the paucity of data in the field and become a starting point for well-organized research in the future." Although each one of us has a special interest in the field of seizures or ICU and follows closely the specific literature, it was the global curiosity to find what really happened during these 5 years—how much more the science has advanced and how much more we know now—that became the motive behind undertaking the daunting task of editing a specialized book like this.

There is new knowledge, indeed: several new studies, new antiepileptic medications, some of them available intravenously, and new published guidelines. This is not distributed evenly, however. Most chapters have undergone extensive revision due to an abundance of new data, few only moderately due to relative paucity of new information. Overall, the book looks fresh and new with the addition of a new chapter on neuromonitoring via continuous EEG in the ICU, complete re-writing of some chapters, addition of new cases with examples of EEGs and MRIs and new tables and figures. Authorities in their fields, Drs Dan Friedman and Larry Hirsch (continuous EEG monitoring), Denise Rhoney (neuropharmacology) and Paul Vespa (non-convulsive seizures in various brain injuries) joined the panel of previous authors to provide pertinent expertise to the readers.

Still a product of collaboration between various experts in the field of intensive care and epilepsy, this new edition is aimed at neurologists, general intensivists, neurosurgeons, and epileptologists. As with the first edition, our hope is that this new book will fulfill the need for more in-depth and specialized knowledge and will help provide specialized management in a very sick patient population.

Detroit, MI
May 2009

Panos Varelas, MD, PhD

Preface to the First Edition

Seizures are devastating events in one's life. Their very presence argues for something being wrong with the brain. In many places of the planet, they are still related to spirits or "sacred illness" and considered as either a curse or a reason for awe. Having been married to an epileptologist and been trained at Yale, one of the best Epilepsy centers in North America, I had a strong exposure and could not escape their spell. I became intrigued by the diversity of their presentation and fascinated by the possibility that various simple or complex behaviors, within the normal or abnormal range, could be explained by such an "obsolete" machine such as the electroencephalograph. Later on, after my training as a neuro-intensivist, my interest grew further while I was trying to find treatable causes in somnolent or comatose patients with various brain injuries in the ICU. This simplistic and mechanistic suspicion, that the patient's clinical status was due to an electrical discharge of the brain, led, I am sure, to several unnecessary requests for EEGs and trials of antiepileptics. Fortunately, I also had some unexpected successes.

Then, I started looking at the issue more closely and had revealing discussions with my peers, especially those who were not neuro-intensivists. To my surprise, two facts emerged: first, many in the ICU community, did not know what to seek, what to expect and how and when to treat; and second, while reviewing the literature, I could not find too much. Most of the articles were reporting small, uncontrolled series or personal experience. Few studies were conducted in the complex environment of an ICU. Very often, as with my personal experience, doubts regarding the epileptic nature of the phenomenon lingered. EEG, the gold-standard test, was difficult to interpret or inconsistently ordered. Seizures could be explained by more than one mechanism in many cases. In other cases, the response could be attributed not so much to the administration of the usual antiepileptics, but to the correction of more systemic derangements. Interaction between ICU medications and antiepileptics were frequent and puzzling to the treating physicians. Several of antiepileptics were either not available for parenteral administration or contraindicated due to specific organ failure. Finally, the newer antiepileptics were not well known and seldom used in the ICU.

Therefore, it did not take me too long to decide about the need for editing a book regarding seizures in the ICU. *Seizures in Critical Care: A Guide to Diagnosis and Therapeutics* is a collaborative effort. Experts in both the ICU and epilepsy fields mainly from North America but also from Europe contributed Chapters in

this book. I tried to confine the content to the most common and interesting in the ICU, however. Norman Delanty's excellent book served as the starting point in many cases, but the scope was different. This book is much more balanced towards central nervous system insults, which can occur in the ICU. I encouraged reference to personal experience and included many real ICU cases with EEGs and neuroimages. Where data were lacking or information was contradictory, a very common situation indeed, the authors were advised to provide raw data and expert advice to the reader. Treatment of ICU seizures, most of the time uniform, is included in a separate Chapter. If more specific treatment is needed, for example pyridoxine for isoniazide-induced seizures, it is mentioned in the appropriate Chapter. Overall, our hope is that this book can serve as a useful aid in the everyday ICU and neurological practice for intensivists, neurologists, neurosurgeons, and any other health care professional or student in this expanding field. Most importantly in my mind, but less directly, it should constitute a testimony of the paucity of data in the field and become a starting point for well-organized research in the future.

Lastly, I would like to dedicate this effort to my parents, my grandfather (the shining star of my life) and all my teachers, who taught me the "ζείν"- living- and "ευ ζείν"- living well- of the ancients. I am also very grateful to all my co-authors, who did an excellent job and especially to my wife, Marianna, for her indirect contribution and support.

Detroit, MI
February 2004

Panos Varelas, MD, PhD

Series Editor's Introduction

The first edition of *Seizures in Critical Care: A Guide to Diagnosis and Therapeutics,* which appeared in 2005, filled an important need in the armamentarium of the neurological, neurosurgical, and medical intensivists who deal with seriously ill patients in the ICU setting. Unlike epilepsy, as it usually presents in the outpatient department, seizures in ICU patients are nearly always secondary phenomena that signify that something is seriously amiss in very ill patients with primary medical or surgical disease. The job of the intensivist is to identify the cause of the seizure or seizures, examine the myriad of potential contributing factors, and provide appropriate management and treatment that takes all aspects of the patient's illness into consideration. As in the first edition, Dr. Varelas and his associates recognize the extreme importance of prompt recognition, diagnosis, and sophisticated management of seizures in this group of seriously ill patients. Dr. Varelas has now recollected his group of contributors and produced a new and up to date compendium of what one needs to know in order to work effectively in this difficult and demanding area. A welcome addition to the new edition is the chapter by Friedman and Hirsch on the role of continuous monitoring in the ICU which is essential for the diagnosis and treatment of nonconvulsive seizures as these may be the most common form of seizures in this setting but are often missed in the evaluation of patients in stupor or coma. Recent technologic advances are described which allow for the simultaneous continuous monitoring of multiple ICU patients using new methods of data acquisition and analysis that allow for rapid and real-time transmission of information to the clinicians caring for the patient. The chapters on seizures due to metabolic causes and drug-induced seizures have new co-authors and have been revised and expanded while the other chapters have all been updated with new information and references. As in the first edition of this book, the issues discussed are all addressed with great common sense and sophistication by the very qualified contributors to this volume.

Daniel Tarsy MD
Professor in Neurology
Harvard Medical School
Beth Israel Deaconess Medical Center
Boston, MA

Contents

Contributors

Andrew Beaumont, MD, PhD
Department of Neurosurgery, Aspirus Spine and Neuroscience Institute, Aspirus Wausau Hospital, Wausau, WI, USA

Lotfi Hacein Bey, MD
Interventional Neuro-Radiology, Radiological Associates of Sacramento Medical Group Inc., Sacramento, CA, USA

Daniel Friedman, MD
Department of Neurology, Comprehensive Epilepsy Center, Columbia University, New York, NY, USA

Romergyko Geocadin, MD
Associate Professor, Departments of Neurology, Anesthesiology-Critical Care and Neurosurgery, Neurosciences Critical Care Division, The Johns Hopkins Hospital, Baltimore, MD, USA

Errol Gordon, MD
Medical College of Wisconsin, Department of Neurology, Milwaukee, WI, USA

Lawrence J. Hirsch, MD
Department of Neurology, Comprehensive Epilepsy Center, Columbia University, New York, NY, USA

Matthew A. Koenig, MD
Assistant Professor, Departments of Neurology, Anesthesiology-Critical Care and Neurosurgery, Neurosciences Critical Care Division, The Johns Hopkins Hospital, Baltimore, MD, USA

Andreas R. Luft, MD
Department of Neurology, University of Tubingen, Tubingen, Germany

Marek A. Mirski, MD, PhD
Director, Neurosciences Critical Care Unit, Departments of Neurology, Anesthesiology, & Critical Care Medicine and Neurosurgery, The Johns Hopkins Hospital, Baltimore, MD, USA

Efstathios Papavassiliou, MD
Assistant Professor, Department of Neurosurgery, Beth Israel Deaconess Medical Center, Harvard Medical School, Boston, MA, USA

Mohammed Rehman, DO
Fellow, Neurocritical Care, Henry Ford Hospital, Detroit, MI, USA

Denise Rhoney, PharmD, FCCP, FCCM
Associate Professor, Pharmacy Practice, Eugene Applebaum College of Pharmacy & Health Sciences, Wayne State University, Detroit, MI, USA
Clinical Associate Professor, Department of Neurology, Wayne State University School of Medicine, Detroit, MI, USA

Jenice Robinson, MD
Department of Neurology, Milton S Hershey Medical Center, Penn State University College of Medicine, Hershey, PA, USA

Marianna V. Spanaki, MD, PhD, MBA
Director, Epilepsy Monitoring Unit, Senior Staff of Neurology, Henry Ford Hospital, Detroit, MI, USA
Associate Professor of Neurology, Wayne State University, Detroit, MI, USA

Jose I Suarez, MD
Director, Vascular Neurology and Neurocritical Care, Associate Professor of Neurology, Department of Neurology, Baylor College of Medicine, Houston, TX, USA

Michel Torbey, MD, MPH, FAHA, FCCM
Director, Stroke Critical Care Program, Department of Neurology, Medical College of Wisconsin, Milwaukee, WI, USA

Panayiotis N. Varelas, MD, PhD
Director, Neuro-Intensive Care Unit, Senior Staff Neurology & Neurosurgery, Henry Ford Hospital, Detroit, MI, USA
Associate Professor of Neurology, Wayne State University, Detroit, MI, USA

Paul Vespa, MD, FCCM
Associate Professor of Neurosurgery and Neurology, Director of Neurocritical Care, David Geffen School of Medicine, University of California, Los Angeles, CA, USA

Zachary Webb, MD, DABPN, DABSM
Medical Director, Sleep Disorders Center, NorthStar Medical Specialists, Bellingham, WA, USA

Eelco FM Wijdicks, MD, PhD, FACP
Professor of Neurology, Mayo Medical School, Medical Director, Neurology–Neurosurgery Intensive Care Unit, Consultant, Department of Neurology, Mayo Clinic, Rochester, MN, USA

Greg A. Worrell, MD
Division of Epilepsy, Department of Neurology, Mayo Clinic, Rochester, MN, USA

Tarek Zakaria, MD
Division of Epilepsy, Department of Neurology, Mayo Clinic, Rochester, MN, USA

Wendy C. Ziai, MD, MPH
Assistant Professor of Neurology, Anesthesia and Neurosurgery, Neurosciences Critical Care Division, Departments of Neurology, Neurosurgery, and Anesthesiology, Critical Care Medicine, The Johns Hopkins Hospital, Baltimore, MD, USA

Chapter 1

Presentation and Pathophysiology of Seizures in the Critical Care Environment: An Overview

Marek A. Mirski

Abstract Seizures represent stereotypic electroencephalographic (EEG) and behavioral paroxysms as a consequence of electrical neurological derangement. Although seizures are often associated with stereotypic convulsive phenomena, in the ICU they are as likely to be subclinical as they are to express muscle contractions or behavioral symptoms. Hence, vigilance is required in the critical care setting. Due to the admission diagnoses and physiological derangements common to critically ill patients, the intensive care unit (ICU) hosts conditions appropriate for the manifestation of the entire spectrum of seizure disorders. Common etiologies of seizures in the ICU are due to primary neurological pathology or secondary to critical illness and clinical management. Alterations in neurotransmitter sensitivity via up- or down regulation of receptors, a decrease in inhibition, alterations in membrane pump functions, all may contribute to the high incidence of seizures in an ICU. Particularly prevalent as precipitants of seizures are hypoxia/ischemia, mass lesions, drug toxicity, and metabolic abnormalities. For optimal treatment, early diagnosis of the seizure type and its cause is important to ensure appropriate therapy. Most seizures and their recurrence are easily treated, and attention is focused on ascertaining the cause and correcting any medical abnormality. Convulsive status epilepticus represents the most feared seizure state, and requires emergent treatment before irreversible brain injury and severe metabolic disturbances occur. Treatment of seizures with anticonvulsants in an ICU is not without risks, and appropriate judgment and selection of therapeutic drugs are important.

Keywords Critical care, Seizures, Pathophysiology, GABA receptors, Nonconvulsive status, Convulsive status epilepticus

1.1. Introduction

Over the past several decades, a collective attempt has been made to define the precise circuitry of brain elements important in seizure expression, together with the physiological mechanisms that ignite these paroxysms. Such answers,

From: *Seizures in Critical Care*: *A Guide to Diagnosis and Therapeutics*: Current Clinical Neurology, Second Edition, Edited by: P. Varelas, DOI 10.1007/978-1-60327-532-3_1,

in theory, would provide the necessary clues to successfully inhibit and prevent the ictal process. Nature, of course, thwarts our attempts to simplify the human condition, and perhaps the most unsettling physiological constraint is our inability to comprehend the intricacies of brain function. Seizures lie within that neurological realm.

In a comparative manner, the complex care environment of the intensive care unit (ICU) is to clinical management what the brain is to human physiology. We still remain appreciably uneducated as to the fundamental physiology that transitions normal brain excitation to ictal behavior. Seizures may occur in any individual, given the appropriate triggers. Our brains normally have a "cloak" of inhibition that aids in protecting us from paroxysmal excitation. Such protective measures become less effective when one is stricken with critical illness, and even less so given additional neurological injury, such as trauma, ischemia, or inflammation,. Coupled with the myriad of physiological derangements that commonly occur in the ICU setting, our risk for seizures becomes unsettlingly high. The ICU is, therefore, both the best environment to gain an understanding into the nature of seizures – based on the incidence, and the worst – because of the multiple and overlapping etiologic factors present. For intensivists, the complexities inherent in an ICU translate to the clinical truism that seizures may appear often and may manifest in severe form, with a few gross noncompliances to routine in-patient management.

As we have come to appreciate, seizures within the ICU are of many types, and the clinical characteristics of each are dependent on the region of brain involved. The term epilepsy, in fact, encompasses a wide variety of recurrent seizure disorders that have been classified in accordance with the location and extent of the seizure process within the brain. Fundamentally, seizures are of two types. They may be partial (focal) in nature or they may be generalized (Table 1-1). This distinction is appropriate for two reasons. First, the extent of cortical involvement differs between the groups. Second, and more important, each seizure type has a neuroanatomical mechanism that is fundamentally distinct. In the examination into their origin, many analytical tools and methods have been used. Surface and depth electroencephalographic recordings have provided the majority of evidence to date, although radiographic techniques such as radionuclide autoradiography, positron emission tomography, computed tomography (CT), and a variety of magnetic resonance (MR) sequence studies have proven to be of substantial value.

The greatest consideration in anatomical mapping has been given to focal epilepsies, in which structural disease is frequently apparent. These seizures display electroencephalographic and clinical manifestations consistent with the involvement of only a portion of the cortex and its corresponding functional systems (Fig. 1-1). Such events are precipitated by local excitatory aberrations of the corresponding cerebral mantle, with the spread typically to adjacent

Table 1-1. Common Presentation of Seizures in the ICU.

Seizure type	Clinical expression
Focal motor	Face or limb motor seizure, no alteration of sensorium
Generalized tonic-clonic	Loss of consciousness, generalized convulsions
Complex-partial	Disturbed sensorium, automatisms common
Non-convulsive status	Disturbed sensorium or loss of consciousness

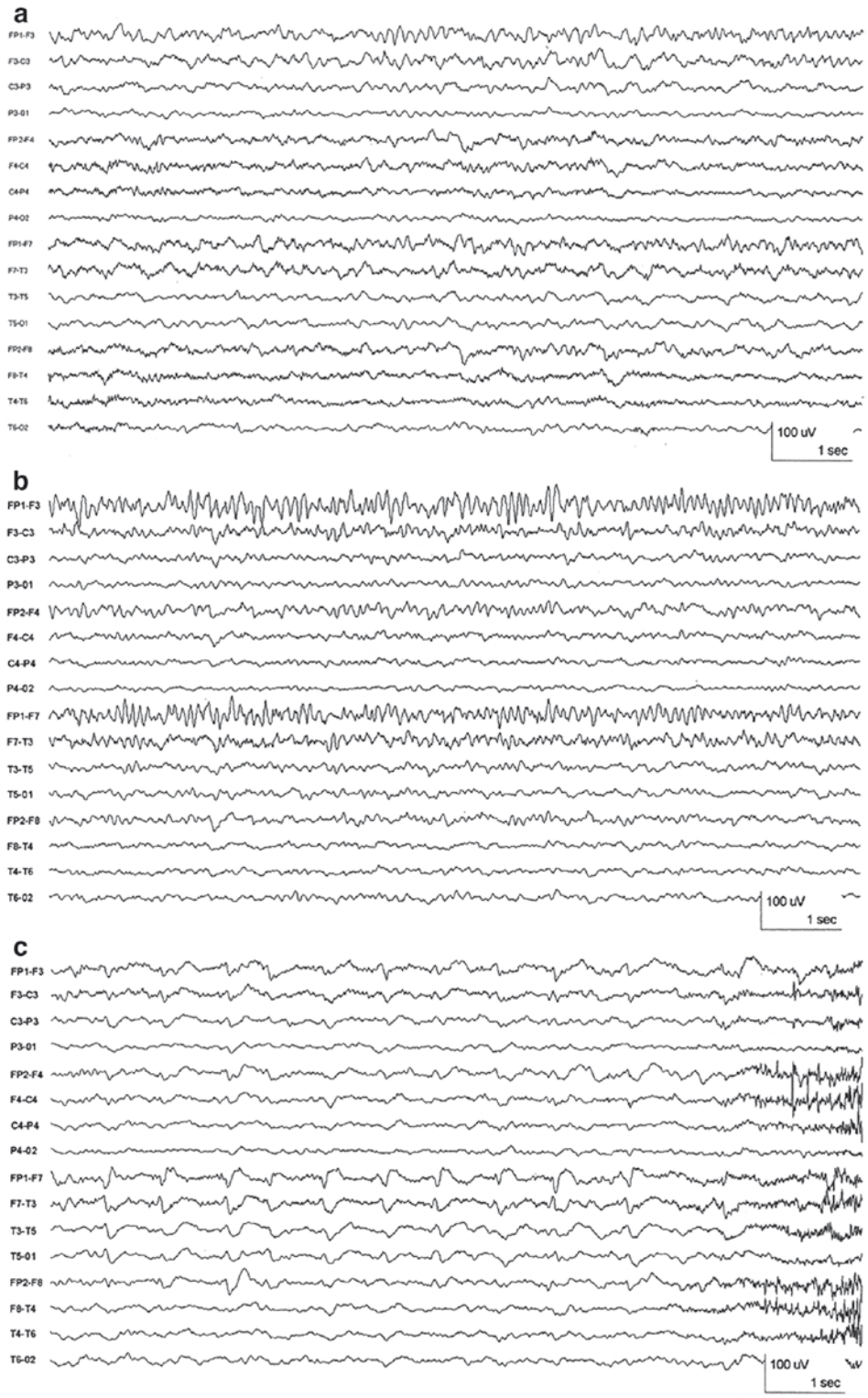

Fig. 1-1. Beginning of a partial (*left frontal temporal*) seizure in a 60-year-old man in complex partial status epilepticus due to vasculitis. (**b**) Thirty seconds after seizure onset. (**c**) The seizure ends with repetitive left frontal temporal sharp waves after 2 min and 7 s. Courtesy of Brenner RP (90)

cortical regions via local synaptic connections. Such ictal events are exemplified by the classic "Jacksonian march", a focal seizure that spreads along the cortical motor strip to progressively excite the neurons that control topographically associated limb musculature.

Other partial seizures, such as many of the temporal epilepsies, are formally described as partial complex because conscious contact with the environment is disturbed. The anatomy involved in this form of epilepsy is more complex than a simple partial seizure because of the recruitment of deeper brain elements that affect our conscious behavior. Most commonly, elements of the limbic brain, usually the hippocampus or amygdala and their connections, play a major role in the expression of these seizures. Automatisms frequent such ictal events – speech or behavioral mannerisms such as lip smacking, blinking, or repetitive hand movements. Such seizures that affect nonmotor regions of the cerebral cortex may be difficult to diagnose unless suspicion is high. Such patients may only appear noninteractive, or in a "fugue" state.

At the other end of the spectrum are the generalized seizures, where consciousness is affected and convulsions may occur throughout the face and extremities. Axial rigidity is not maintained, and the patient will fall if standing. Generalized seizures commonly begin with a focal cortical nidus, from which proceeds rapid spread of ictal activity. This "secondary" generalization may, in some circumstances, be too rapid for the electroencephalogram (EEG) to detect (Fig. 1-2). As a group, generalized seizures likely spread via cortical networks or cortical–subcortical circuits. The "primary" generalized seizures (example: absence epilepsy or primary tonic-clonic seizures) probably utilize brainstem/subcortical structures in the mediation and propagation of the paroxysmal activity (1–5).

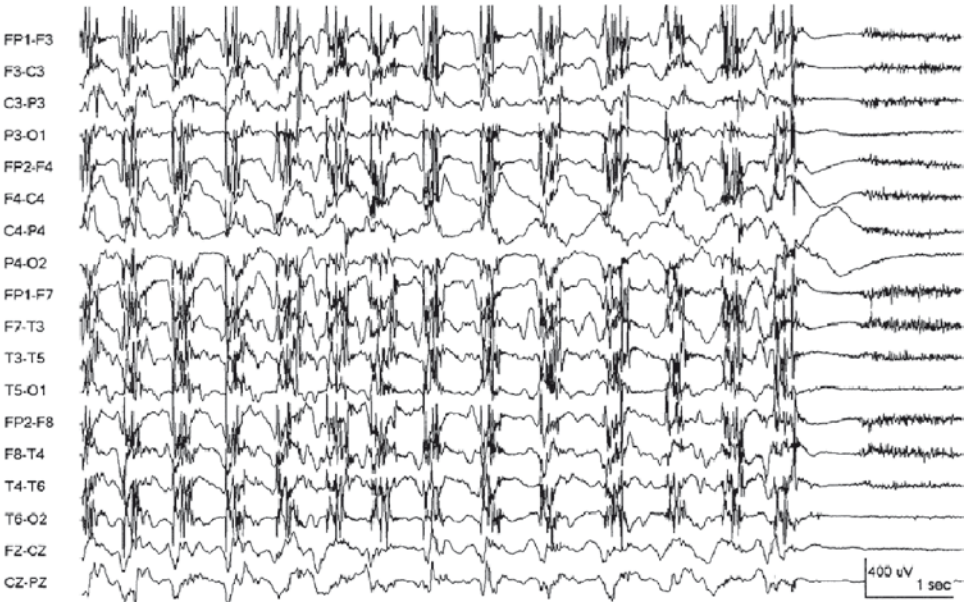

Fig. 1-2. Generalized spike and wave, best seen in the midline electrodes, with prominent superimposed repetitive muscle artifact during the clonic phase, followed by postictal suppression in a 22-year-old woman with a primary generalized tonic-clonic seizure. Courtesy of Brenner RP (90)

No cortical nidus is identified, and the deeper cerebral elements are the likely culprits in the initiation, or at least early propagation of these events (6–13). These primary generalized seizures are exemplified by bilaterally synchronous and symmetrical epileptiform discharges on EEG and clinical behavior typically characterized by loss of consciousness and generalized convulsive or paralytic motor phenomena. Although it is commonly stated that bilateral cortical involvement in a synchronized ictal EEG renders loss of consciousness, it has been demonstrated that there are exceptions (14, 15). Indeed, such descriptions support the fact that even during expression of "generalized seizures", there are brain regions seemingly uninvolved in the paroxysmal activity, and can maintain circuit integrity for a wakeful state. In the majority of instances of generalized seizures, no diffuse or focal brain disease or generalized metabolic disturbance can be convincingly demonstrated. Non-convulsive generalized seizures may also occur, and are more difficult to diagnose. As discussed later, such seizures often complicate the management of the comatose ICU patient.

In the intensive care unit (ICU) setting, seizures are a common neurological complication in both medical and post-surgical patients, and commonly arise from co-morbidities associated with the ICU experience (Table 1-2).

Table 1-2. Complications of Critical Illness – Seizure Predisposition.

Hypoxia/ischemia
Drug/substance toxicity
Antibiotics
Antidepressants
Antipsychotics
Bronchodilators
Local anesthetics
Immunosuppressives
Cocaine
Amphetamines
Phencyclidine
Drug/substance withdrawal
Barbiturates
Benzodiazepines
Opioids
Alcohol
Infection & Fever
Metabolic abnormalities
Hypophosphatemia
Hypocalcemia
Hypoglycemia
Renal / hepatic dysfunction
Surgical injury (craniotomy)

Most ICU seizures occur in patients never having had a prior episode, or having neurological pathology as part of the primary admitting diagnosis. A review by Bleck et. al. noted that approximately 12% of patients admitted with nonneurological primary diagnoses incurred neurological events during their critical illness (16). Of these, seizures (28.1% incidence) closely followed metabolic encephalopathy (28.6%) as the leading neurological complication. Status epilepticus, the diagnosis most associated with seizures and the ICU is, in fact, a rare admission diagnosis (0.2%) as compared to the incidence of seizures as a complication (3.3%). Since seizures occur most often in non-primary neurological patients, it is important for the general clinician, intensivist, and consulting neurologist to be cognizant about the potential for seizures in the ICU and be aggressive in treating them.

Regardless of the seizure type, the medical management in an ICU and the environment itself unfortunately present unique challenges and difficulties with regards to the etiology, diagnosis, and treatment of seizures. Patients are critically ill, and the common scenario of multi-system organ dysfunction presents a variety of potential etiologies for cerebral disturbance, often predisposing to seizures. Also, treatment with sedatives, as a means to provide comfort to the patient, and paralytic agents to optimize therapy alike, hinder the neurological examination (17). Many pharmaceuticals used in an ICU, particularly the psychotropic medications, antibiotics, stimulants, and others may also lower seizure threshold (18, 19). Anticonvulsants and other medications may alternatively sedate the patient or enhance toxic responses, further delaying neurological recovery from the seizure episode (20). Such difficulties may lead to additional diagnostic studies and prolongation of ICU stay. Seizures may also accompany conditions that render the patient into a coma state – such as severe encephalopathy, trauma, or stroke (21–28), or following seemingly uncomplicated procedures in healthy patients. For example, of late, the phenomenon of Posterior Reversible Encephalopathy Syndrome (PRES) has been reported more frequently as a consequence of labor and delivery, and seizures can be one of its prominent manifestations (29). Recurrent or continuous seizure activity may prevent arousal, and requires EEG assessment for correct diagnosis. More seriously, recurrent seizures and status epilepticus (SE) are more difficult to suppress than simple focal or generalized convulsions and can be life-threatening when they occur as complications of primary neurological or other visceral organ disease. Finally, the ICU itself is an environment with considerable electrical field dispersion, often preventing optimal EEG recording.

The need to diagnose and effectively treat recurrent seizure activity is imperative. Multiple seizure events or convulsive SE may lead to acidosis, hyperthermia, rhabdomyolysis, and trauma with consequent higher morbidity and mortality (30, 31). Loss of protective airway reflexes is common in patients with prolonged or recurrent seizures, and promotes the likelihood of pulmonary aspiration. The duration of seizures of more than one hour is an independent predictor of poor outcome (odds ratio of almost 10) (31). Prolonged seizures increase the risk of cerebral damage due to excitotoxicity, intracellular Ca^{++} accumulation and apoptosis, epileptogenic synaptic reorganization and sprouting, and the depletion of energy stores with inhibition of protein and DNA synthesis (32).

1.2. Cellular Pathphysiology of ICU Seizures

Fundamentally, despite numerous phenotypic expressions of seizures and epilepsy syndromes, the manifestations of the ictal process emanate from a few common cellular mechanisms and brain loci. The cerebral cortex is the nidus for most clinically evident seizures; the hippocampus, the most rudimentary cortical element of the medial temporal lobe, also falls into that category. Regarding subcortical structures, it is well known that the thalamus plays a substantive role in mediating the paroxysms and supporting the hypersynchronous, rhythmic EEG activation. Specific research effort has prominently identified all three locations in seizure mechanisms, and implicated a variety of neuronal and glial functions (10, 33–36).

As evidenced by the cortical EEG, the fundamental marker for an epileptic paroxysm is the interictal spike, which is the electrical fingerprint of the intracellular paroxysmal depolarizing shift or PDS (Fig. 1-3). The interictal spike is generated by a synchronous firing of a network of local neurons, coupled

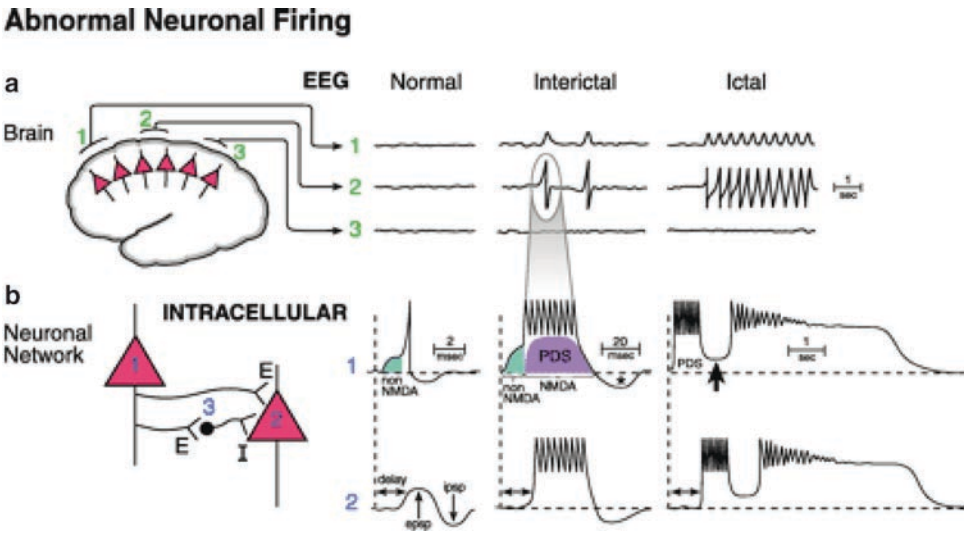

Fig. 1-3. Abnormal neuronal firing at the levels of (**a**) the brain and (**b**) a simplified neuronal network consisting of two excitatory neurons (90, 91) and an inhibitory interneuron (1). EEG (*top set of traces*) and intracellular recordings (*bottom set of traces*) are shown for the normal (*left column*), interictal (*middle column*), and ictal conditions (*right column*). Numbered traces refer to like-numbered recording sites. Note time scale differences in different traces. (**a**) Three EEG electrodes record activity from superficial neocortical neurons. In the normal case, activity is low voltage and "desynchronized" (neurons are not firing together in synchrony). In the interictal condition, large "spikes" are seen focally at electrode 2 (and to a lesser extent at electrode 1, where they might be termed "sharp waves"), representing synchronized firing of a large population of hyperexcitable neurons (expanded in time below). The ictal state is characterized by a long run of spikes. (**b**) At the neuronal network level, the intracellular correlate of the interictal EEG spike is called the "paroxysmal depolarization shift" (PDS). The PDS is initiated by a non-NMDA-mediated fast EPSP (*blue*) but is maintained by a longer, larger NMDA-mediated EPSP (*red*). The post-PDS hyperpolarization (*) temporarily stabilizes the neuron. If this post-PDS hyperpolarization fails (*right column, thick arrow*), ictal discharge can occur. The lowermost traces, recordings from neuron 2, show activity similar to that recorded in neuron 1, with some delay (double-headed arrow). Activation of inhibitory neuron 3 by firing of neuron 1 prevents neuron 2 from generating an action potential (the IPSP counters the depolarization caused by the EPSP). If it does reach firing threshold, neuron 2 then can recruit additional neurons, leading to an entire network firing in synchrony (seizure). Illustration by Marcia Smith and Alan Michaels. Courtesy Strafstrom (91)

with periods of inhibition via K^+ current-activated hyperpolarization. Neurons that are particularly readily disposed to such activity are the pyramidal cells of cortical layer V and the CA3 neurons within the hippocampus (37). These cells are synaptically linked to regional neurons that amplify the excitation within a synaptic network. The paroxysmal discharge may be induced by a local increase in excitation, a decrease inhibitory neurotransmission, or alteration in Na^+ or K^+ current conductance (38). Excitation is classically derived from direct stimulation of N-methyl,D-aspartate (NMDA) receptors or enhancement of synaptic transmission via reduction of K^+ current. Reduced inhibition may stem from antagonism of gamma-amino-butyric acid (GABA) activity at its receptor or decreasing GABA binding through chemical means, such as a reduction of local Mg^{++} (39–42).

The interictal spike may be effectively transitioned to an array of several spikes, or a "burst", by the presence of local burst-generating cells. These are made possible by persistent Na^+ and Ca^{++} slow action potential currents that function primarily in the dendritic formations, promoting prolonged depolarizations in the neuron soma (41, 43). The bursts appear to further manifest when there is alternating depolarization between the dendrites and soma (44). Network modeling of hippocampal cells has reproduced the EEG events of a tonic-clonic seizure (45, 46). The high frequency firing tonic component is triggered by prolonged somatic depolarizations, and the slower synchronous clonic seizure results from rhythmic bursting of slow-channel dendrite depolarizations. Continued depolarization of the neuronal membrane (contrast to the brief depolarization of a PDS), is responsible for the maintenance of successive rapid discharges inherent in a stereotypic seizure. Recurrent after discharges, as occur during a clonic seizure, are perpetuated by a reduction of the hyperpolarizations that occur following aberrant paroxysms such as the interictal spike.

Now that the susceptible tissue has undergone epileptiform transformation, the propagation to larger cortical terrain, or even to generalize, requires vital network pathways and connections (47, 48). On a regional scale, ictal events may spread by disruption of the local chemical environment, such as alterations in K^+ or Mg^{++}. Such spread is not very rapid, estimated at 50–200 mm/sec (49). Clinically important seizure propagation must clearly utilize synaptic transmission via networked connections. Even ectopic transmission has been proposed as a means to further enhance the spread or continuation of the ictal state (50). Such cortico-cortico or subcortico-cortico circuitry has only been occasionally identified (10, 35, 50–52) (example, Fig. 1-4).

We do know from clinical experience that there are many pathological conditions inherent in ICU patients – particularly those with primary cerebral disturbance, that predispose to seizures (Table 1-3). However, very little is known concerning the contribution of regional pathology on the predisposition to seizures, despite ready acknowledgement that injured regions of brain following a stroke or head injury appear more prone to paroxysms than native cortex (53). Similarly, brain tissue adjacent to "irritative elements" such as neoplasms with associated edema or vascular malformations has been associated with a high risk of manifesting seizures. The mechanisms leading to enhanced susceptibility have only recently been forthcoming (Table 1-4) (54, 55).

It is clear from work on cerebral neoplasia that tumors may have intrinsic cellular properties inciting an epileptogenic focus (56, 57). Other consequences of a mass lesion that impacts regional blood flow and supply (such as tumors

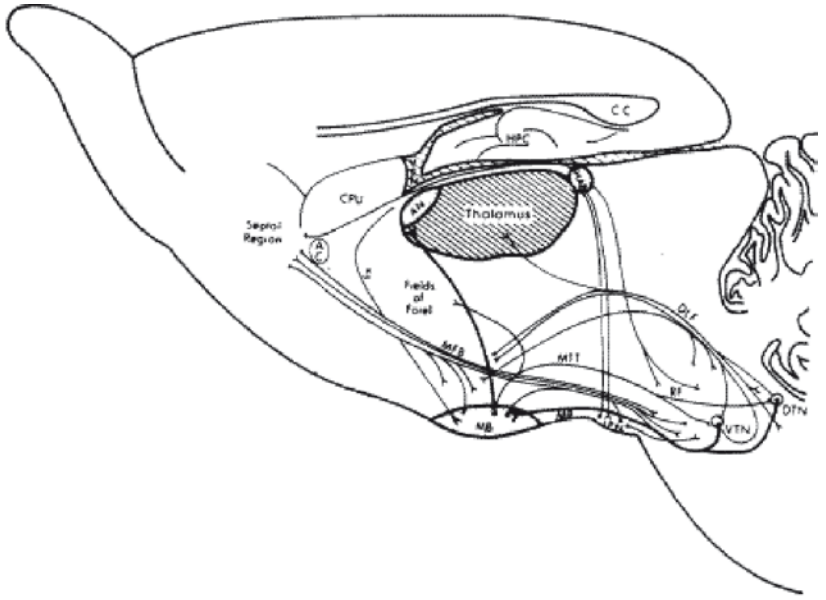

Fig. 1-4. Sagittal illustration of rat brain depicting one of the few identified subcortical pathways participating in the early propagation of experimental generalized seizures. In this case, the expression of seizures induced by the chemical convulsant pentylenetetrazol has been shown to be modulated by the perturbation of neuronal activity within the path from the brainstem (ventral & dorsal tegmental nuclei) synaptically linked to the hypothalamus, anterior thalamus (AN), and cingulate gyrus (31). Recent clinical trials of deep brain stimulation of AN for refractory epilepsy have been very promising (Medtronic-SANTE Trial). *MB* mammillary bodies, *MTT* mammillotegmental tracts, *VTN* ventral tegmental nuclei, *DTN* dorsal tegmental nuclei, *MFB*: median forebrain bundle; *CPU* caudate-putamen, *HPC* hippocampus, *DLF* dorsal longitudinal fasciculus; *MP* mammillary peduncle

Table 1-3. Common Etiologies of Seizures in the ICU.

Neurological pathology	
	Neurovascular
	Stroke
	Arteriovenous malformations
	Hemorrhage
	Tumor
	Primary
	Metastatic
	CNS infection
	Abscess
	Meningitis
	Encephalitis
	Inflammatory disease
	Vasculitis
	Acute disseminated encephalomyelitis
	Traumatic head injury
	Contusion
	Hemorrhage
	Primary epilepsy
	Primary CNS metabolic disturbance (inherited)

Table 1-4. Pro-Convulsant Mechanisms Inherent in Cerebral Neoplastic and Vascular Malformations.

Intrinsic epileptogenic cellular properties (tumors)
Local impaired vascularization/ischemia
Denervation hypersensitivity
Axonal & synaptic plasticity
Decrease in regional GABA
Increase in local glutamate
Alteration of electrolyte ions – Mg^{++}
Increase in regional Fe^{++}

Adapted from Beaumont and Whittle (93).

Table 1-5. Intracranial Pathology and Relative Risk for Seizures.

Pathology	High risk
Stroke	Hemorrhagic
	Large cortical involvement
	Acute confusional state
Intracranial tumor	Cortical – primary
	Cortical – metastatic
Traumatic head injury	Cerebral contusion
	Acute subdural (SDH)
	Depressed skull fracture
	Penetrating missile injury
	Evacuation/chronic SDH

or AVMs) are the potential for local tissue ischemia, denervation hypersensitivity, alteration in neural plasticity, and disequilibrium of the local microchemistry – GABA, glutamate, Mg^{++}, etc (58–61). Some evidence also suggests alterations in intercellular iron ions (Fe^{++} or Fe^{+++}) may exist and predispose to seizures. Aside from the putative intrinsic epileptogenic characteristics of certain tumor types themselves, the pro-convulsant features listed above that have been associated with tumors and AVMs, may likely apply to cerebral tissue affected by head injury, stroke, and inflammatory conditions (Table 1-5). In the following chapters, there will be a detailed discussion relating to the specific etiologies and therapies for seizures occurring in the ICU arena.

1.3. Clinical Manifestations and Diagnosis

A focal or generalized seizure commonly lasts for several seconds or up to 1–2 min. During this period, alterations in hemodynamics and respiratory indices are typical in generalized convulsions, with increases usually recorded in heart rate and blood pressure. Ventilation may be impeded in the latter seizure type, with desaturation noted on pulse oximetry, often with excessive salivation. Interestingly, although grunting and gasping are encountered during a

generalized tonic-clonic seizure, patients only rarely incur an aspiration event. If one should occur, it is almost always of the patient's oral secretions rather than gastric contents. Therefore, patient care during a violent convulsion is focused on protecting the patient from extremity injury, biting of the tongue, and maintenance of a clear airway during prolonged seizures. Brief desaturations are the rule, and require no special intervention. For the vast majority of simple convulsive episodes, protection of the airway beyond what is described above, or frank ventilatory support, is not indicated. A depressed sensorium is common following a generalized convulsion, requiring several additional minutes before baseline is re-established. Focal or generalized seizures may also lead to post-ictal focal deficits (Todd's paralysis), lasting up to several hours. These deficits are especially common in patients with pre-existing subtle weakness from a mass lesion or stroke, and seizures can accentuate these pre-convulsive neurological impairments. In contrast to generalized convulsive episodes, patients with focal seizures are fully cogent during their attack, and those with complex-partial seizures typically return rapidly to their baseline neurological state.

Most seizures that occur in an ICU setting, likely manifest as generalized tonic-clonic convulsions, including secondary generalization, with some reports observing approximately 90% of the presenting seizure as of this variety (16, 26). Focal seizures comprise the majority of remaining behaviorally disturbing seizure types. These data suggest that recognition of a seizure in the ICU is rarely a diagnostic dilemma. Although uncommon, patients who do present with complex-partial or other nonconvulsive seizures (9%) may be considerably more difficult to diagnose, especially in a critical care setting where sedative medication is often administered. That said, there is increasing concern that nonconvulsive SE (NCSE) may be much more prevalent in ICU patients. Recent data suggests that 5%–10% of ICU comatose patients were in NCSE (62). Other investigators have evidence to suggest that the incidence of non-convulsive seizures is alarmingly high, up to 34% of neurological ICU patients, and it is only for a lack of monitoring that these seizures are not detected (63, 64).

Specifically within the ICU setting, there have been reports of an interesting phenomenon known as "stimulus-induced seizures", whereby relatively minor tactile stimulation to the patient evokes a rhythmic, ictal EEG discharge and may be accompanied by overt motor clonic activity (65, 66). Hirsch et al have described these events as "stimulus-induced rhythmic, periodic, or ictal discharges" (SIRPIDs) (66). Such evoked responses are usually focal in nature. There are reports that focal stimulation may induce bilateral periodic discharges (PEDS) and a mild arousal response in comatose patients (67).

Besides overt behavioral manifestations, the scalp EEG is the diagnostic test of choice. Even when a seizure is noted by obvious clinical expression, evaluating the treatment success according to the presence or absence of motor paroxysms or level of consciousness may be occasionally misleading. Treatment of motor convulsions alone may be insufficient to prevent the continuation of seizure activity. The persistence of electrographic status without convulsions (NCSE) has been observed in 14% of patients treated for convulsive SE (68). Conversely, improvement in the neurological examination is often a poor clinical assessment tool, as 87% of patients successfully treated for convulsive SE and 100% of patients treated for NCSE remained comatose 12 h following the

initiation of therapy (69). Therefore, it cannot be over emphasized that electrical monitoring of ICU patients is crucial in settings where seizures may be a complicating feature of critical illness. Unless a seizure fully resolves and the patient returns to an alert, cognitive baseline, an EEG is highly useful, if not mandatory to exclude ongoing ictal activity.

1.4. Overview of Status Epilepticus

Status epilepticus represents a distinct seizure phenomenon. Not simply a prolonged seizure, SE represents a reconfiguration of the excitatory and inhibitory network of normal brain (70). Most focal seizures do not secondarily spread to produce a generalized event because of local inhibitory circuitry (GABA-mediated) that prevents enlargement of the ictus. As seizures continue, it is known that a breakdown occurs within this cortical "inhibitory surround", thus making it easier for seizure activity to spread. In addition, the inhibitory events which assist in terminating the seizures also become disturbed. Thus, recurrent or prolonged seizures induce a positive feedback loop that help sustain, rather than inhibit further ictal activity. In essence, "seizures beget seizures" (70).

Exactly when a prolonged seizure or set of recurrent seizures is deemed to have become "SE" is a question that continues to evolve. Historically, since the 1960's, the minimum time of unremitting seizures before SE said to occur by experts in the field was arbitrarily assigned to 30 min. This included a single generalized seizure lasting greater than 30 min, or a group of repetitive seizures between which the patient had not fully recovered. Given the discussion regarding the risk of early neuronal injury, and a desire to adequately treat this disorder prior to irreversible cerebral insult, shorter seizure epochs have been more recently emphasized as SE. Based on the typical seizure duration of 1–2 min., it is reasonable to consider as SE any seizure events greater than 5–10 minutes in length. Such is now the tenet of the American Academy of Neurology and the American Epilepsy Society. There are several reports describing seizures of 10–29 min duration that have had spontaneous resolution without therapy, but consensus is that these represent a small population. It is strongly felt that a high risk-benefit ratio exists in not treating such patients as SE. If treatment was required to "stop" the clinically obvious seizure, EEG correlation again is advocated if the patient has not returned to their pre-ictal, alert condition.

There are three main subtypes of SE, two of which are prominent in the ICU. Generalized Convulsive SE (GCSE) represents the classic motor SE (Fig. 1-5). These seizures may be overt or have subtle motor manifestations, especially if the SE is prolonged. By far, GCSE is the most commonly reported SE subtype. Focal Motor SE (FMSE) or epilepsy partialis continuans, is relatively uncommon, and rare in the ICU. Continuous motor twitching of a single limb or a side of the face is most frequently observed. These seizures can be difficult to control with medications. It is not clear whether prolonged FMSE results in substantive injury to the cerebral cortex. Thus, reasonable attempts at control are advocated, but high-risk therapies such as induced pharmacological coma are rarely involved. Nonconvulsive SE (NCSE) is often used as an umbrella term incorporating a wide spectrum of continuous non-motor seizures. As a group, they may encompass primary generalized SE, such

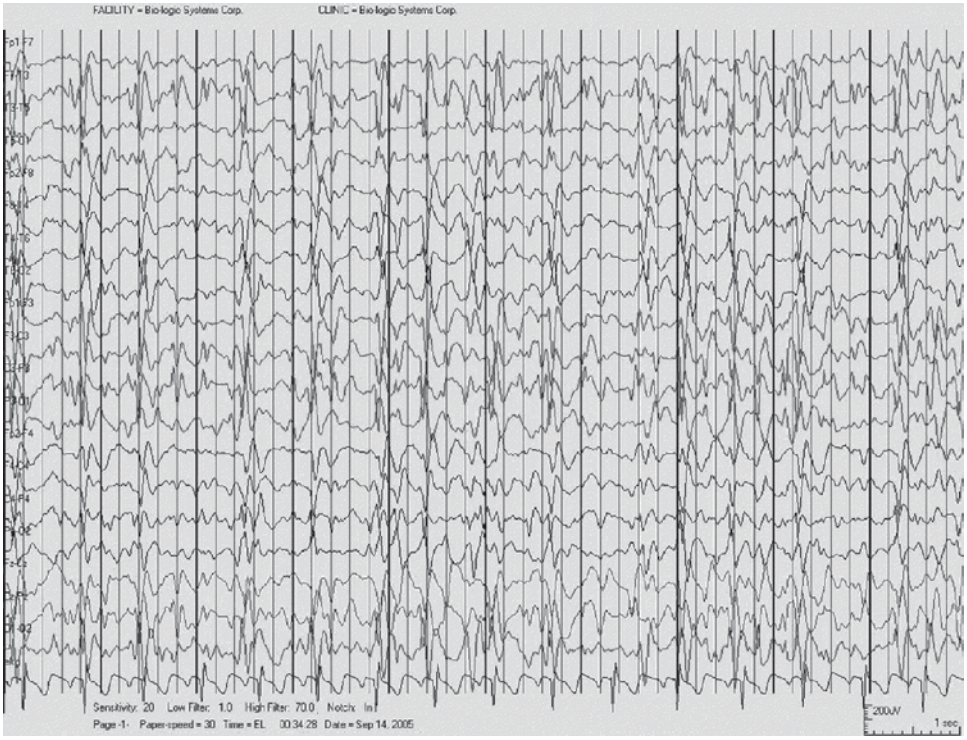

Fig. 1-5. This EEG shows diffuse multifocal or generalized spikes or spike waves that then pervade the recording during non-REM sleep, and 1.5–2.0 Hz generalized spike waves. Courtesy Kaplan (92)

as absence SE, which has a very stereotypic EEG, to secondary generalized seizures with variable EEG features (Fig. 1-6). Other terms within NCSE are complex-partial SE, subtle SE, nontonic-clonic SE,and subclinical SE. The hallmark is a diminishment of the neurological exam secondary to the seizure, but the patient may present clinically anywhere along the spectrum between being awake/ambulatory to coma. The true incidence of this subtype of SE is unknown and likely under recognized (64, 71). Pertinent to the ICU setting, a recent trend ascribes the label of NCSE to patients having suffered from severe anoxic/ischemic encephalopathy, when characteristic EEG spikes are present. When such EEG findings, consisting of bilateral periodic lateralizing epileptiform discharges (PLEDS), are present along with the appropriate clinical history, they portend a poor neurological outcome (72).

Although there is a strong consensus in aggressively treating GCSE (73–78), there is mixed opinion as to the proper management of NCSE (63, 68). These seizures are diagnosed by recurrent paroxysmal or epileptiform bursts on the cortical EEG. In the purest form, without prior evidence of cerebral injury or mass lesion, NCSE is typically benign. Apart from the altered cognition during the seizure that may be disabling, there is no evidence that permanent morbidity has been attributed to this form of SE. Thus, therapy should be directed towards chronic prevention of the attacks. In the ICU, however, most forms of NCSE are associated with a history of moderate to severe cerebral injury, as following an anoxic-ischemic event or trauma. Although associating the effects of NCSE on direct neuronal injury is difficult in this setting, most

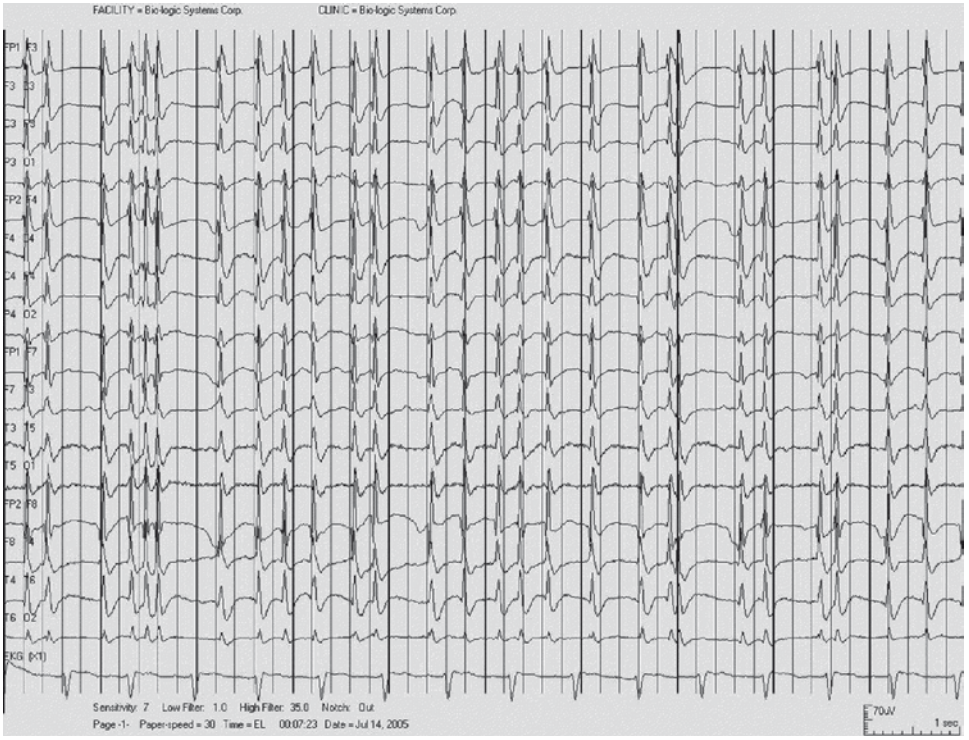

Fig. 1-6. This EEG shows generalized, but predominantly synchronous frontal epileptic discharges typical of GNSE. Courtesy Kaplan (92)

Table 1-6. Typical EEG Presentation of GCSE and NCSE SE.

Classic GCSE	Generalized spike or sharp wave pattern –begins from a normal background rhythm. SE is characterized by an unremitting spike activity or, more commonly, a crescendo-decrescendo pattern of major motor ictal periods interspersed with lower voltage paroxysmal activity. No abrupt termination or "postictal depression" is observed as following simple seizures.
NCSE	EEG is variable, with a number of EEG patterns being recognized. Generally, seizures such as complex-partial status resemble their non-SE counterparts.

epileptologists would agree that in such scenarios the presence of continuous paroxysmal activity may accentuate injury incurred by the primary insult. Therefore, it is felt prudent to attempt therapy as rapidly as is feasible. To what degree one should attempt to abolish the EEG paroxysms remains unclear, although even the induction of barbiturate coma has been performed.

As may be expected, monitoring by EEG is critical to the accurate diagnosis of SE, and for monitoring of the therapeutic response. This is especially true for both NCSE and prolonged convulsive SE, where there is a paucity of physical findings and the EEG may be the only effective tool for diagnosis (75–80). Table 1-6 lists common EEG features of GCSE and NCSE. For ongoing SE, EEG (preferably continuous) is mandatory to ensure effective treatment. Commonly, convulsive SE is incompletely treated with residual subtle EEG seizures or NCSE, despite cessation of motor ictal activity. Some clinical

reports suggest residual electrographic seizures in almost 50% of patients with GCSE, and a 10–20% incidence of NCSE in those patients treated for GCSE with cessation of motor seizure activity (68).

1.5. Paroxysmal Lateralizing Epileptiform Discharges (PLEDS)

The significance of paroxysmal lateralizing epileptiform discharges (PLEDs) has been debated since their first designation in the early 1960's, but the fact not in dispute is their frequent attendance in ICU patients. Although not rigidly defined, PLEDs have been ascribed to the presence of spikes, sharp waves, or mix of sharp-spike waves that may have coincident slow waves that together appear on the EEG at regular, periodic intervals (Fig. 1-7) (81). Mostly described in patients with cortical injury, PLEDs have also been associated with patients with epilepsy syndromes and following bouts of severe seizures, such as SE. Ischemic stroke appears to be the most frequent etiology, but other brain conditions such as hemorrhage, neoplasms, cortical infection and inflammation, and even metabolic disturbances have been linked to this EEG phenomenon (82).

The underlying pathophysiological mechanisms remain unclear, but their similarity to the interictal spike suggests that similar chemical/membrane disturbances underlying the PDS may be fundamental. An interesting observation

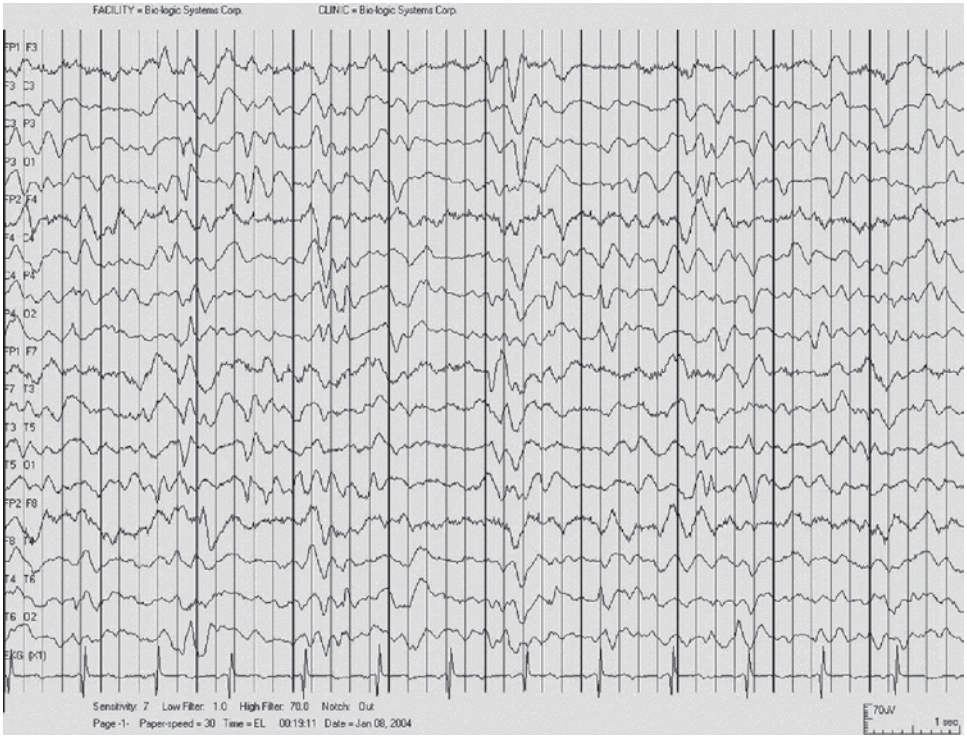

Fig. 1-7. This EEG shows bilateral, independent PLEDs occurring over the left and right frontal regions, without clinical correlate. Courtesy Kaplan (92)

has been made where clinically occurring PLEDs were linked to basal ganglia circuit function (83). This is of interest as it links subcortical activity with PLEDs, and thus connects this epileptiform phenotype with the basal ganglia association with seizures (84).

Many consider PLEDs a cerebral response to an acute focal process, although these paroxysms may last for several years if a stroke or mass lesion remains a physiological irritant. Although structural injury is the greatest stimulant for development of PLEDs, metabolic or diffuse alteration of cerebral function may be an etiologic factor in some patients (85). The presence or absence of coincident paroxysmal bursts leads to a subcategorization of "simple or proper PLEDs" or "PLEDs plus" (86). The disappearance of PLEDs either spontaneously or with anticonvulsant therapy has been well documented (87, 88).

Lacking consensus is the attribution of PLEDS to an active ictal state. It is clear that these discharges may come in the setting of a diagnosis of seizures, or simply with a structural lesion. Data does not appear to support definite conclusions that may be drawn from their presence, such as patient clinical outcome or as further risk for seizures (89). Some have observed that PLEDS may occur secondary to tactile stimulation in comatose patients associated with a clinical arousal response (67).

1.6. Conclusion

Seizures occurring in the ICU setting are more difficult to prevent, diagnose, and treat effectively than those manifesting outside the ICU or hospital. Particularly challenging is the diagnostic component of seizure management, especially when only subtle clinical evidence is present, and the EEG is not conclusive. The use of a variety of medications and the clinical management in an ICU all tend to lower, rather than elevate seizure threshold. A high index of suspicion is warranted by the intensivist, and early use of EEG surveillance can be vital in early detection. Treatment of seizures in an ICU setting can also be challenging, even when not dealing with SE. The ability to recognize and treat seizures is critical, however, as there exists clear evidence for potential grave neurological injury when seizures persist as SE. However, the treatment of seizures itself may impose new patient toxicity, and requires appropriate toxicity/benefit evaluation, as well as proper drug selection. Lastly, confronting the etiology of the seizures, assessing the risk for future episodes, and understanding treatment options can greatly assist in formulating their acute ICU and future therapeutic management.

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