Epilepsy Case Studies

Pearls for Patient Care

William O. Tatum
Joseph I. Sirven
Gregory D. Cascino
Editors

Springer

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ISBN 978-3-319-01365-7 ISBN 978-3-319-01366-4 (eBook)
DOI 10.1007/978-3-319-01366-4
Springer Cham Heidelberg New York Dordrecht London

Library of Congress Control Number: 2013951512

Printed on acid-free paper

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

This book is dedicated to patients with epilepsy and their families—thank you for your education about seizures and about life.

William O. Tatum IV

Preface

Sir William Osler said, "To study the phenomenon of disease without books is to sail an uncharted sea, while to study books without patients is to not go to sea at all."* This book is about 40 people whose lives took a different course after they were affected by seizures and epilepsy. The chapters in this book represent case histories drawn from "real-life" experiences in people with seizures. The intent of presenting these patient histories in a case-based format is designed to stimulate the same deductive reasoning that is commonly used when seeing epilepsy patients in the clinic. The use of neuroimaging and neurophysiology in the study of patients with epilepsy has become a staple with which the diagnosis and treatment of epilepsy has become inextricably intertwined. Therefore, the correct interpretation of these studies is essential to reach the correct diagnosis and treatment. Following the clinical scenario composed of a wide variety of epilepsy cases, questions are posed to organize the reader's thoughts in addressing each case. Questions that revolve around each patient include commonly asked questions such as, "How does this test help us with the diagnosis?" and "What is the precise relationship of the patient's seizures to their overall neurological condition?" The most poignant questions include, "How does this information help us to devise a treatment plan?" and "What do we know about the anticipated course and prognosis?" The questions raised in each section incorporate answers to these questions about diagnosis, treatment, and prognosis where the a knowledge base exists. They are addressed in a segment of the book that focuses on a discussion of the facts of the case. Where it is possible, these discussions rely upon the latest medical evidence to support the responses. At the end of each case a few salient citations are included. Our hope to provide an overview of the topic and search for an expanded bibliography, if they so desire.

We learn from every patient. Our "take-home" messages are encapsulated in the form of clinical pearls that shape the basis of our understanding. Furthermore, these pearls of wisdom guide our decision-making in the approach to treatment of future patients with similar case scenarios. There is simply no written text that can replace the knowledge that is derived from hearing and seeing our patient and what they tell us. Our overreliance and overuse of "tests" will never replace the clues that our patients give us when we perform the neurological history and examination.

The field of epileptology encompasses some of the most dynamic and dramatic conditions that a Neurologist will face. Little is more surprising in the field of Medicine than the spontaneity and unpredictability of seizures. Case Studies in Epilepsy will aid in selecting the approach to a clinically based problem list in a style that we hope stimulates reasoning in a style that is fun. From cases that include first onset seizure to drug-resistant epilepsy, from seizures stemming from unknown causes to those produced by a brain tumor, from infancy to the elderly, diagnostic dilemmas and treatment challenges exist and require an individualized approach. Standard and novel diagnostic associations with seizures including genetics and autoimmunity are addressed in addition to nonmedical treatment options including epilepsy surgery, neurostimulation, dietary control, and alternative medicine. These topics are well represented by 40 illustrative case studies contained in this book. An introduction to some of the emerbing treatments such as newer anti-seizure drugs, neurostimulators, and minimally-invasive brain surgeries for epilepsy are included. The cases themselves, serve as the platform to highlight and encompass the broad group of the epilepsies including those with genetic, structural-metabolic, and unknown causes. These cases were obtained from expert epilepsy clinicians at the Mayo Clinic. It is widely known that even in the most productive academic circles, even the most educated in epilepsy centers may be heard to say, “I remember that I once had a case of …”.

*Osler W. Books and men. Boston Med Surg J. 1901;144:61.

Jacksonville, FL, USA William O. Tatum IV, D.O.

Acknowledgment

I am grateful to my colleagues at the Mayo Clinics for both the opportunity to work with them and to learn from them. This multiauthored enterprise-wide work has been compiled by many outstanding epileptologists that have contributed freely and generously of their time. It serves as a testimony to their dedication to the field of epilepsy. Each author has presented a specific vignette that represents a patient who suffered from an individual affliction of epilepsy. It is not the symptom that is remembered, but rather it is the person who imprints the case on our minds. To a large degree, our collective experience in patient care has been shaped by the unique qualities of a single patient whose story has impacted our own lives. These individuals quickly come to mind when we need an example to serve as a prototype for a certain syndrome or situation.

One of my favorite mentors first taught me that it is the needs of the patients that come first in delivering the best neurological care possible. That people are behind the symptoms of their illness and that treatment begins with compassion and advocacy by a human touch. The stigma and painful lack of predictability with seizures that patients and their families endure is something that most of us will hopefully never know. The cases described in this book while presented in a didactic fashion lack the emotional coloring behind each case too shallow to be appreciated. I hope that the readers of this book will never experience a seizure. Instead, I hope that these 40 stories, which are drawn from real-life experiences, can portray the breadth and individuality of epilepsy and therein provide education and compassion that in some way is able to help at least 1 person with seizures.

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Chapter 1
Epileptic Spasms

Elaine Wirrell

Case Presentation

A 7-week-old female presented with a 2-week history of recurrent, brief spells that consist of bilateral arm and leg flexion (left more so than right). She also had head flexion to the left and leftward eye deviation. Each event lasted less than 1 s, but these occurred several times a day in clusters that lasted up to 10 min. Events were particularly prominent shortly after waking. She was diagnosed with a seizure disorder and started on Topiramate by her local pediatric neurologist. The events persisted without a change in event frequency, despite dose increases to 20 mg/kg/day.

She was the product of a healthy term pregnancy to a 31-year-old G1P0 mother. The delivery was a normal spontaneous vaginal delivery with a birth weight of 3,600 g. She was discharged from the hospital at 2 days of age and was well without incident until 5 weeks of age. Her previous family history was unremarkable.

The general examination was unremarkable. Her weight, height, and head circumference were all at the 25th percentile of growth for her age. A thorough examination of her skin was performed, including a normal evaluation with a Wood's lamp. There were no neurocutaneous lesions. She was alert and attentive at her neurological examination. Her cranial nerves were normal. Her motor examination demonstrated that she had mild hypotonia in her left upper extremity and tended to use it less than her right arm. Sensory examination revealed that she had symmetrical withdrawal to noxious stimulation. No pathological cerebellar functions or reflexes were evident. Brain MRI (Fig. 1.1) and EEG (Fig. 1.2) were also subsequently obtained.

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W.O. Tatum et al. (eds.), *Epilepsy Case Studies: Pearls for Patient Care*,
DOI 10.1007/978-3-319-01366-4_1,

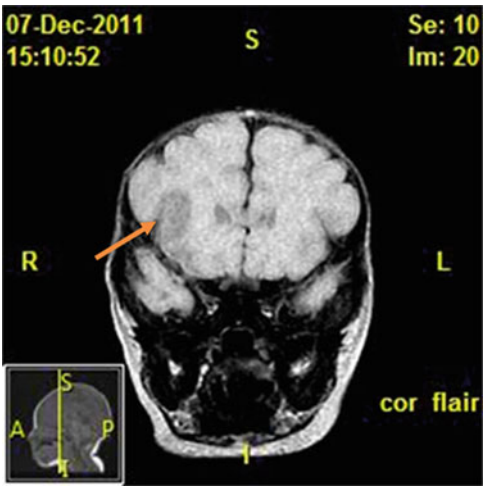

Fig. 1.1 Coronal T1 image of brain MRI at 6 weeks of age. Note the hypointensity in the right frontotemporal region involving insular cortex (*arrow*)

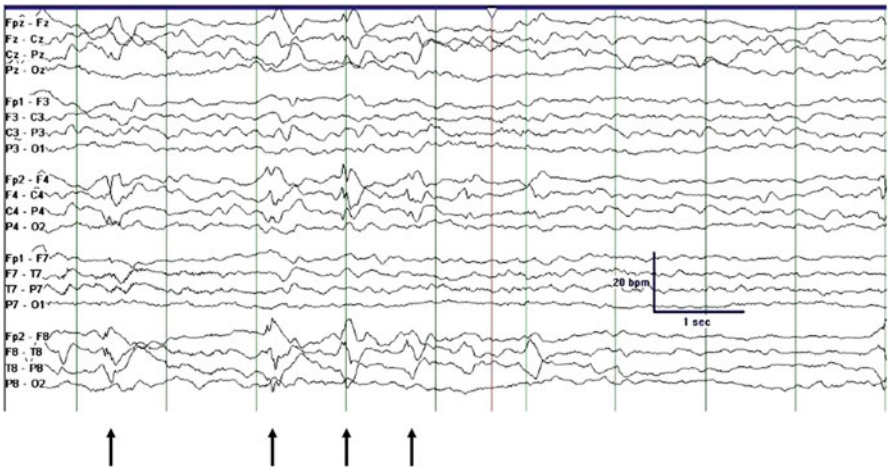

Fig. 1.2 Interictal EEG demonstrating right frontal-temporal epileptiform discharges (*arrows*). Sensitivity 10 μV/mm, filter settings 1–70 Hz, display speed 60 mm/s

Clinical Questions

1. What specific type of spell is she presenting with clinically?
2. What is the most likely etiology for these events?
3. What does her neuroimaging and EEG demonstrate?
4. How do you classify dysplastic cortical malformations?
5. How should she be managed?

Discussion

1. She is presenting with epileptic spasms (ES), which have a focal component. Epileptic spasms are seen most commonly in the first year of life and characteristically occur in clusters, as in this child's case. They are most commonly associated with West syndrome, though they may appear independent of a syndromic association. West syndrome is characterized by the triad of (a) spasms, (b) hypsarrhythmia on the EEG, and (c) intellectual disability, and is most commonly present between 2 and 24 months of age. ES may also be associated with Ohtahara syndrome (early infantile epileptic encephalopathy), which frequently occurs with focal seizures. In Ohtahara syndrome, onset of spasms typically occurs at a younger age than West syndrome, often in the first 2 months of life. Most infants with Ohtahara syndrome will be found to have a structural brain abnormality; however, in approximately 10 % of cases, a genetic etiology (particularly a mutation in *STXBP1*) is responsible. Children with Ohtahara syndrome are encephalopathic and show a burst-suppression pattern on EEG.
2. An underlying etiology can be identified in approximately 80 % of cases; however, the etiologies are diverse. They include structural abnormalities of the brain that include, but are not limited to, prior injury, tuberous sclerosis, and malformations of cortical development (MCD). In addition a genetic predisposition or chromosomal etiology (Trisomy 21, *CDKL5* mutation, *ARX* mutation, etc.) or metabolic disorders (mitochondrial cytopathies, pyridoxine dependency, etc.) may be involved.
3. The brain MRI scan that was done at 6 weeks of age showed a T1 hypointensity in the right anterior insular cortex. This is most likely due to a focal MCD. In early infancy, focal MCD are seen as T1 hypointensities without a corresponding T2 hyperintensity. Due to ongoing myelination, such malformations can be very challenging to visualize between 4 and 24 months. After 2 years, MCD can be detected by the more typical features of cortical thickening, blurring of the gray–white junction, abnormal gyral or sulcal patterns, or T2 hyperintensity.

   Her interictal EEG pattern showed sharp waves rising from the right frontotemporal region. Ictal EEG later confirmed seizure onset that arose from the same area. Her EEG at this time was not consistent with either a hypsarrhythmia (note the absence of high-voltage EEG) or a burst-suppression pattern. Because of the features on EEG, a more definitive diagnosis of West or Ohtahara syndrome could not be made.
4. A clinicopathological classification system has been proposed, which divides these lesions into the following groups:

   FCD type I: Abnormal cortical layering that either compromises the radial migration and maturation of neurons (FCD type Ia), the 6-layered tangential composition of the neocortex (FCD type Ib), or both (type Ic)

   FCD type II: A malformation that presents with disrupted cortical lamination and specific cytological abnormalities. FCD type IIa has dysmorphic neurons

without balloon cells, while FCD type IIb has dysmorphic neurons with balloon cells.

FCD type III: Cortical lamination abnormalities associated with a principal lesion: FCD type IIIa (hippocampal sclerosis), FCD type IIIb (tumor), FCD type IIIc (vascular malformation), FCD type IIId (other lesion acquired early in life).

FCD types II and III may appear morphologically on the brain MRI. FCD type I has histological features that may only be evident on histopathological examination and not the brain MRI. However, EEG may reveal focal or epileptiform abnormalities in FCD type 1 that can reflect this MCD.

5. Epileptic spasms may occur independent of an association with either of the above epilepsy syndromes. Nevertheless ES are usually indicative of a severe epilepsy that is likely to be drug resistant. Epileptic spasms can be challenging to treat. Despite the fact that her EEG does not yet show hypsarrhythmia, treatment should be initiated with vigabatrin, ACTH, or high-dose prednisolone. She was treated with vigabatrin 140 mg/kg/day and became seizure free. During that time, she also progressed developmentally in an age-appropriate manner. Unfortunately, her seizures recurred at 7 months. Despite addition of high-dose levetiracetam, focal seizures with left-sided motor symptoms occurred several times per day. She regressed in her development. She then underwent resection of the right frontal MCD. Focal resections have been effective in patients with ES as it was in her case rendering her seizure free. The pathology was consistent with FCD IIA (without balloon cells).

Clinical Pearls

1. Epileptic spasms are most common in infancy. They usually occur in clusters. Prompt diagnosis and effective therapy are crucial, as they are frequently associated with an epileptic encephalopathy with either failure of developmental progression or even regression.
2. Structural lesions may present with ES in infancy. They are frequently refractory to medical therapy. The occurrence of focal ES with coexistent focal seizures or a focal abnormality on the neurological examination or EEG suggests the presence of a focal lesion.
3. Focal MCD can be very challenging to visualize on MRI between 4 and 24 months due to the ongoing myelination process. Children with drug-resistant epilepsy should be considered for epilepsy surgery.
4. A referral for an epilepsy surgical assessment should be considered in a young child with drug-resistant seizures who has failed two antiepileptic medications due to a lack of efficacy. Such referral is urgent if there is evidence of developmental regression.

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Chapter 2
Pyridoxine-Dependent Epilepsy

Lily Wong-Kisiel

Case Presentation

A 2-day-old male neonate became increasingly irritable and developed repetitive twitching in the eyelids, face, and limbs around 24 h of life. He was the full-term product of non-consanguineous parents following a normal pregnancy and uneventful spontaneous vaginal delivery. Investigations for infectious etiologies including blood and urine cultures as well as cerebrospinal fluid analysis were unrevealing. An MRI of the brain was normal. Prolonged video EEG demonstrated voltage suppression of the background activity. Irritability and recurrent irregular lightening-like jerks became noted several hours after birth that were associated with electrographic bursts of high-voltage epileptiform discharges on the EEG suggesting myoclonic seizures (Fig. 2.1). Myoclonic seizures remained refractory to conventional antiseizure drugs (ASDs). Pyridoxine 100 mg IV resulted in almost immediate cessation of his myoclonic seizures. In addition, gradual return of continuous EEG background activity was noted. Extensive investigations to find metabolism inborn error or genetic etiologies later revealed an elevated plasma pipecolic acid level and an elevated urinary α-aminoadipic semialdehyde level that supported a diagnosis of pyridoxine-dependent epilepsy.

Clinical Questions

1. What are the differential diagnoses for neonatal seizures?
2. What is the significance of the EEG suppression-burst pattern in a neonate?
3. What should be expected from pyridoxine challenge?

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W.O. Tatum et al. (eds.), *Epilepsy Case Studies: Pearls for Patient Care*,
DOI 10.1007/978-3-319-01366-4_2,

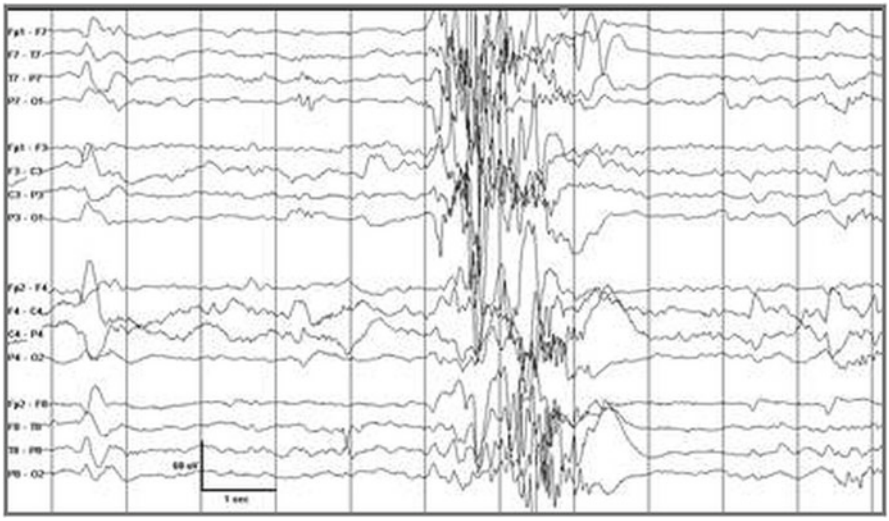

Fig. 2.1 Scalp ictal EEG showed background suppression (note scale legend) with paroxysmal bursts of high-voltage spikes, polyspikes, and sharp waves associated with myoclonic jerks

4. What causes pyridoxine-dependent epilepsy?
5. What causes pyridoxine-deficient seizures?

Diagnostic Discussion

1. Neonatal seizures occur in three per 1,000 live births and commonly imply a serious neurological disease. The most common cause is hypoxic-ischemic encephalopathy, though other causes include stroke, metabolic derangements (hypoglycemia, hypocalcaemia), prenatal and neonatal infections, malformation of cortical development, inborn errors of metabolism, and benign epilepsy syndromes. Neonatal seizures are usually subtle clinically and are characterized by bicycling movements, sucking, smacking, tonic eye deviation, and autonomic phenomena such as apneic episodes. Clonic seizures and myoclonic seizures comprise nearly 50 % of neonatal seizures; however, generalized tonic–clonic seizures rarely occur due to immature myelination. The diagnosis of seizures in the newborn can be challenging because many suspected clinical seizures have no electrographic correlate and many electrographic seizures have no clinical correlate (electroclinical dissociation). Polygraphic video-EEG is the standard for neonatal monitoring and includes monitoring of respirations, electrocardiogram, eye movement, and chin myogram to help differentiate epileptic seizures from benign neonatal movements such as jitteriness, posturing, and sleep myoclonus.

2. The suppression-burst pattern is characterized by low-amplitude background activity that is less than 10–15 mV and that alternates with bursts of asynchronous, high-voltage activity (Fig. 2.1). Suppression-burst pattern does not suggest a specific etiology, but is associated with severe encephalopathy. In the absence of a clinical course suggesting hypoxic-ischemic encephalopathy, severe metabolic derangement, medication effects, and hypothermia, the suppression-burst pattern in a term neonate suggests an early-onset epileptic encephalopathy. Ohtaraha syndrome (early infantile epileptic encephalopathy with suppression-burst pattern) and early myoclonic encephalopathy can be differentiated based upon different seizure manifestations and their EEG patterns. Ohtaraha syndrome is characterized by frequent tonic seizures that are often associated with a structural etiology. Most of these infants develop West's syndrome and have epileptic spasms, developmental delay, and hypsarrhythmia. The presence of myoclonic seizures and suppression-burst pattern in the case scenario describes a neonate with early myoclonic encephalopathy. Early myoclonic epilepsy is linked to the inborn errors of metabolism. Suppression-burst pattern occurs in both wakefulness and sleep in Ohtahara syndrome, in contrast to early myoclonic epileptic encephalopathy where the suppression-burst pattern is almost limited to sleep.
3. Vitamin B6 includes pyridoxine, pyridoxamine, pyridoxal, and their related 5′-phosphate esters. Pyridoxine is available from nutritional sources. Pyridoxal-5-phosphate is the biologically active form of vitamin B6 and is an essential cofactor for several neurotransmitter synthesis and amino acid metabolism. Pyridoxine challenge is recommended for neonates and young children with epilepsy that is refractory to ASDs. A single dose of pyridoxine 100 mg intravenously is given to see if the typical, dramatic cessation of seizures occurs. Apnea and respiratory depression have been reported after intravenous pyridoxine, especially when higher doses are utilized. Therefore, cardiorespiratory monitoring and the need for respiratory support should be anticipated. An absence of an EEG abnormality that fails to normalize or the lack of seizure control does not rule out pyridoxine-dependent epilepsy. A trial of oral pyridoxine 30 mg/kg/day (200 mg/day in neonates and 500 mg/day in adults) may be continued until pyridoxine-dependent epilepsy can be excluded by biochemical or mutation analysis. A diagnostic withdrawal of pyridoxine resulting in seizure recurrence or seizure resolution after resumption of the vitamin B6 supports the diagnosis of pyridoxine-responsive epilepsy.
4. Pyridoxine-dependent epilepsy is characterized by myoclonic, clonic, and focal or generalized tonic–clonic seizures that are resistant to conventional ASDs, yet respond to vitamin B6. Pyridoxine-dependent epilepsy is an autosomal recessive disorder due to mutations in the *ALDH7A1* gene. The enzyme that is deficient is α-aminoadipic semialdehyde dehydrogenase (antiquitin). A deficiency results in the accumulation of α-aminoadipic semialdehyde, piperideine-6-carboxylate, and pipecolic acid with a secondary deficiency in pyridoxal-5-phosphate (active form of vitamin B6). Elevation of plasma pipecolic acid and urinary and CSF α-aminoadipic semialdehyde act as diagnostic markers. Pyridoxal-5-phosphate is

an essential cofactor in neurotransmitter synthesis (especially GABA) and amino acid metabolism. The treatment for pyridoxine-dependent epilepsy is lifelong supplementation with pyridoxine. Some patients with *ALDH7A1* gene mutation do not have a clear response to pyridoxine, but show a response to folinic acid. Folinic acid 3–5 mg/kg/day may be considered in those neonates who have an incomplete pyridoxine response. Infants who do not respond to pyridoxine should have a trial of pyridoxal-5-phosphate. Other pyridoxine- or pyridoxal-5-phosphate-responsive epilepsies include neonatal/infantile hypophosphatasia, familial hyperphosphatasia, and nutritional vitamin B6 deficiency.

5. An acquired deficiency in pyridoxine can also cause seizures, but unlike pyridoxine-dependency where continuous replacement is needed with pyridoxine deficiency, a single dose of vitamin B6 is sufficient. Reduced pyridoxine intake from malnutrition or a diet limited to grains increases the risk for pyridoxine deficiency. In infants, pyridoxine deficiency can cause growth delay, weight loss, irritability, anemia, and seizures. Adults may have other manifestations such as seborrheic dermatitis and cheilosis. Medications such as isoniazid or intestinal malabsorption and hepatic or renal disease can cause increased excretion of pyridoxine. Sensory polyneuropathy from pyridoxine deficiency typically affects the feet and legs and is characterized by paresthesias and burning dysesthesias. The finding that some children with epileptic spasms responded to pyridoxal-5-phosphate prompted a separate group of patients with pyridoxine-responsive epilepsy. The active form was found to have greater activity for more pediatric patients with inborn errors of vitamin B6 metabolism.

Clinical Pearls

1. Clinical features of pyridoxine-*dependent* epilepsy in the neonatal period include irritability, status epilepticus, and medically refractory epilepsy. Neonatal seizures associated with pyridoxine-dependent epilepsy may mimic hypoxic-ischemic encephalopathy, infectious etiologies, and inborn errors of metabolism, but unlike pyridoxine *deficiency*, it requires lifelong supplementation with vitamin B6.
2. A suppression-burst pattern on the EEG in a neonate in the absence of medication effect, metabolic derangements, and hypothermia is associated with epileptic encephalopathy and implies a poor prognosis.
3. The lack of an immediate clinical or EEG improvement to pyridoxine IV challenge does not exclude pyridoxine-dependent epilepsy. Therapeutic trial of pyridoxine and diagnostic pyridoxine withdrawal along with biochemical or mutation confirmation and pyridoxine withdrawal can support the diagnosis of pyridoxine-dependent epilepsy.
4. Antiquitin deficiency is the main cause of pyridoxine-dependent epilepsy, which results in accumulation of neurotoxic organic acids and secondary deficiency of pyridoxal-5-phosphate.

5. Mental retardation and neurological deterioration in newborns may occur if pyridoxine administration is delayed. Respiratory precautions are warranted during initial and higher dose pyridoxine use.

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Chapter 3
Febrile Seizures

Harry S. Abram

Case Presentation

A 2-year-old female presents to a local emergency room following a 20-min generalized tonic-clonic seizure. The parents witnessed the seizure begin without warning. The seizure consisted of rhythmic jerking of the body and extremities without lateralizing features that could be identified. After termination of the event, the child was listless and without spontaneous interaction. She was the full-term product of non-consanguineous parents following a normal pregnancy and uneventful spontaneous vaginal delivery. With the exception of this event, she has been a normal healthy child with age-appropriate development. She had received all of the required immunizations for the usual childhood diseases. She was not taking any medications at the time of her seizure. This young girl had been noted to be "sick" prior to the onset of the seizure and had been exposed to other children who had recently experienced the flu. Upon assessment, in the emergency room, she was initially very irritable and uncooperative. She had a temperature of 103° and an apparent inflammation of the right tympanic membrane upon examination. Following ibuprofen, her temperature resolved. Within 60 min she was cooperative and had a normal neurological examination.

Previous family history was notable for an older brother who had a similar event with a fever and was diagnosed with a fever-related seizure. In addition, a maternal aunt experienced a similar episode and later developed epilepsy as a young adult. The parents were very frightened by the seizure and worried about the onset of more seizures, epilepsy, and the death of their daughter.

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W.O. Tatum et al. (eds.), *Epilepsy Case Studies: Pearls for Patient Care*,
DOI 10.1007/978-3-319-01366-4_3,

Clinical Questions

1. What are febrile seizures (FS) and how are they classified?
2. How should a child with febrile seizures be evaluated?
3. What is the reoccurrence risk of a second FS after the first? What is the risk of developing epilepsy in later childhood or adulthood? What is the risk of brain damage or death?
4. What are the treatment options?
5. What is the latest genetic research in FS?

Diagnostic Discussion

1. Febrile seizures are seizures that occur in febrile children between the ages of 6 months and 5 years who do not have an intracranial infection, metabolic disturbance, or history of afebrile seizures. This is the most common seizure disorder in early life, affecting 2–5 % of all children. Peak incidence is between 18 and 24 months. FS are subdivided into two categories: simple and complex. Simple FS last for less than 15 min, are generalized, and occur once in a 24-h period in a neurologically normal child, whereas complex FS are prolonged (>15 min), are focal, occur more than once in 24 h, or are in a neurologically abnormal child.
2. Diagnostic evaluation of a child with an FS should be initially directed at determining the source of the fever. Meningitis should be considered in any febrile child. A lumbar puncture should be strongly considered in any child less than 12 months. The decision in older children should be based upon their medical history and clinical examination. The physician should pay special attention to prior treatment with antibiotics and documentation of appropriate immunizations. Typical meningeal signs such as stiff neck may not be reliably present under the age of 2 years.

   An EEG is not indicated in a neurologically healthy child with a simple FS. There is no evidence to suggest that routine blood studies will benefit the evaluation of the child with a simple FS. These should be obtained only as indicated after appropriate histories and careful physical examinations. In a similar manner, neuroimaging should not be performed in the routine evaluation of simple FS. CT scanning is associated with radiation exposure that may escalate future cancer risk. MRI is associated with risks from required sedation and high cost.
3. After a single FS, the risk of a second is approximately one-third. This risk may range from approximately 15 to 75 % depending on the number of risk factors (see Table 3.1).

   The risk of developing subsequent epilepsy is only minimally greater than the risk to the general population (5–7 % versus 1 %). However, various risk factors have been noted to increase this risk: children with complex FS, onset younger than 12 months, a family history of epilepsy, abnormal neurological examination,

Table 3.1 Reported risk factors for recurrent febrile seizures

Age < 15 months
First-degree relative with febrile seizures or epilepsy
Low-grade fever at seizure onset
Short duration of fever prior to seizure
Daycare attendance
Complex febrile seizures
Developmental delay

or abnormal neuroimaging. With multiple risk factors, the risk of developing epilepsy by the third decade is 17 % versus 2.5 % if there are no risk factors. There is no evidence that the use of prophylactic anticonvulsant medication with FS can prevent the later development of epilepsy. There is also no evidence that simple FS causes structural damage to the brain. It is most likely that the increased risk of epilepsy in this population is the result of genetic predisposition. There has never been a reported death from a simple FS.

There has been a suggested link between FS and a later development of temporal lobe epilepsy, but that exact role remains unclear. Some studies have suggested that the development of hippocampal sclerosis has been noted to occur following prolonged FS in young infants. This may be due to increased cellular changes in a more vulnerable location.

4. Despite the frequency of simple FS, there is no uniform opinion about management options. Although there is evidence that both continuous antiepileptic therapy with phenobarbital, primidone, or valproic acid and intermittent therapy with oral diazepam are effective in reducing the risk of recurrence of further FS, the potential toxicities associated with antiseizure drugs outweigh the relatively minor risks associated with simple FS. As such, long-term therapy is typically not recommended. In situations where parental anxiety is severe, seizures are prolonged or recurrent, or families have limited access to health care, intermittent oral or rectal use of a benzodiazepine at the onset of febrile illness may be effective in preventing recurrence. Although antipyretics may improve the comfort of the child, there is no data that this will prevent further febrile seizures.
5. Disorders involving voltage-gated ion channels have been increasingly noted in neurological disease. Greater than 300 mutations involving the *SCN1A* gene, which is the gene controlling sodium channels, have been implicated in a broad spectrum of mild to very severe epileptic syndromes. The *SCN1A*-related seizure disorders have many presentations and include FS, generalized epilepsy with FS plus (GEFS+), Dravet syndrome (severe myoclonic epilepsy of infancy), Doose syndrome (myoclonic-astatic epilepsy), Lennox–Gastaut syndrome, and vaccine-related encephalopathy. These disorders are important to recognize due to genetic implications (autosomal dominance), alteration in anticonvulsant management (avoiding medications with sodium channel blocking properties), and family counseling.

Clinical Pearls

1. Though FS are frightening events for families, the crux of treatment is addressing the etiology of the febrile illness and counseling families of the benign nature and excellent prognosis of FS. Long-term anticonvulsants are not typically recommended. Intermittent use of a benzodiazepine may be appropriate in certain clinical situations.
2. Counsel parents of children who might be at an elevated risk for an initial febrile seizures, as well as recurrent FS. Genetic factors are important. FS are two to three times more common in children whose parents or siblings experienced FS.
3. Epilepsy is uncommon following FS, with the risk only being marginally greater than the normal population.
4. Follow updated published guidelines from the American Academy of Pediatrics for guidance regarding evaluation and management of simple febrile seizures. There are no published guidelines for complex FS. These should be evaluated and managed more cautiously with greater consideration for LP, EEG, and neuroimaging.
5. Consider molecular genetic testing for mutations in *SCN1A* in children who present with repetitive febrile seizures in the first year of life and proceed to develop intractable generalized epilepsy with neurological regression.

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Chapter 4
Childhood Absence Epilepsy

Raj D. Sheth

Case Presentation

A 7-year-old female presented with brief episodes of staring that lasted for a few seconds. These episodes recurred multiple times throughout the day. She was taken to her primary care physician when she suddenly stopped walking in the middle of a busy intersection. She appeared to abruptly freeze and was motionless until her parents noticed that she was lagging behind. They returned to assist her safely across the street. According to her parents, she had been an excellent student. However, recently they had been receiving notes from her teachers reporting that she had been periodically staring into space. She appeared as if she were daydreaming. They were significant enough to interfere with her ability to attend to her classes. The symptoms became especially alarming when she experienced an episode associated with urinary incontinence at school. She had no other complaints and was developmentally and neurologically normal on examination. Laboratory studies were unremarkable and she was referred for a routine EEG (Fig. 4.1).

Clinical Questions

1. Does this EEG support a particular clinical diagnosis?
2. What is the relationship between staring spells and epilepsy?
3. What is meant by a "typical" absence seizure?
4. What are the ASDs that are used to treat CAE?
5. What is the anticipated clinical course and prognosis?

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W.O. Tatum et al. (eds.), *Epilepsy Case Studies: Pearls for Patient Care*,
DOI 10.1007/978-3-319-01366-4_4, © Springer Science+Business Media New York 2014

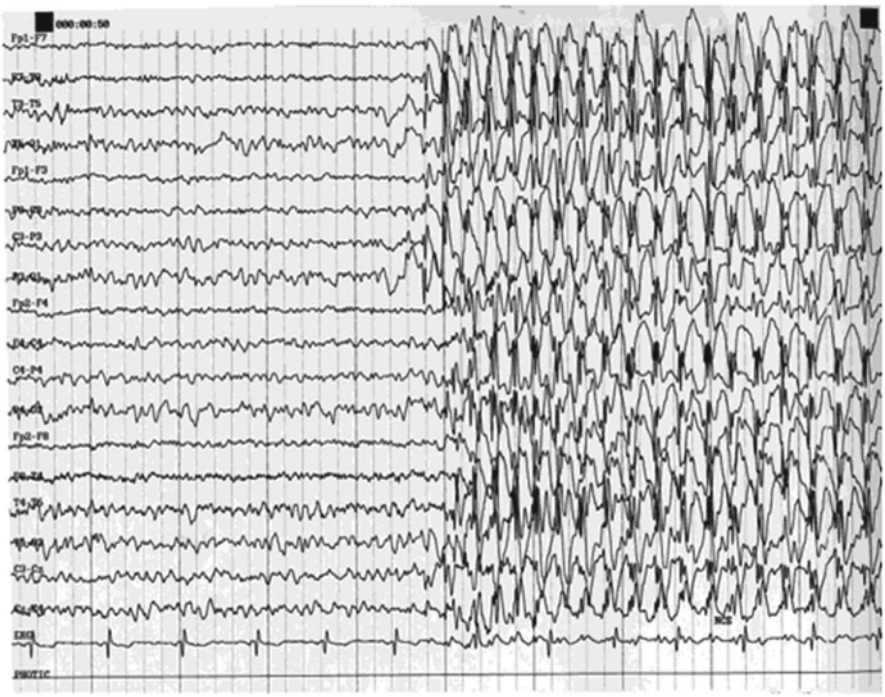

Fig. 4.1 EEG shows 3.5–4 Hz bilaterally synchronous and symmetric anterior-predominant generalized spike-and-wave discharges lasting 5 s that were precipitated by hyperventilation

Diagnostic Discussion

1. The EEG shows a burst of 3.5–4 Hz generalized spike-and-wave discharges. In the context of a staring episode, this EEG would be diagnostic of a typical absence seizure. This finding supports a clinical diagnosis of childhood absence epilepsy in this patient. CAE involves dysfunction of the thalamic relay neurons, thalamic reticular neurons, and cortical pyramidal neurons. About 5–10 % of all childhood epilepsies involve absence seizures. *Typical* absence seizures involve staring with brief impairment of consciousness and are associated with 3 Hz generalized spike-and-slow-wave discharges on the EEG that are activated by hyperventilation and intermittent photic stimulation. Seizures may often be missed due to the subtlety of the clinical features and brevity of the attack. Special response testing methods may be required to demonstrate impaired consciousness. In addition to a blank stare, there are often other associated clinical manifestations, such as automatisms, eyelid myoclonus, and autonomic disturbances.
2. The EEG may be diagnostic in absence epilepsy or spells when electrographic seizures are captured. The generalized discharges may become fragmented and last for shorter periods of time during sleep, which suggests a focal mechanism

for staring. Differentiating absence seizures from focal seizures and episodic non-epileptic daydreaming is crucial for effective counseling and treatment. The EEG is crucial to address the mechanism that defines the episode. Ictal recordings support CAE when the 3 Hz GSW pattern is evident, when there is localization-related epilepsy and focal seizures, when focal epileptiform discharges are present, when there are non-epileptic staring spells, and when the EEG is devoid of epileptiform features entirely during the spells.

3. Atypical absence seizures are much less common than typical absence seizures. They are often encountered in patients with Lennox–Gastaut syndrome and maybe the EEG correlate that accompanies drop attacks. Clinically, atypical absence seizures are associated with developmental delay or mental retardation. In contrast, the mental function in patients with typical absence seizures is normal. EEG is often key in differentiating atypical absence from typical absence seizures. The presence of diffuse slow (<2.5 Hz) spike-and-waves (SSW) on the EEG defines "atypical" absences. In addition to SSW, the background electrocerebral activity is abnormal with diffuse slowing of the background intermixed with theta or delta waves.
4. Treatment of absence seizures is frequently effective. Monotherapy is preferred. The most effective ASDs used to treat absence epilepsy is valproate (VPA) although it is most likely associated with adverse events. Lamotrigine appears to have less adverse effects, but is less effective than VPA or Ethosuximide (ETH). ETH appears to be the best choice of ASDs when treating absence seizures. This is due to the optimal balance between efficacy and adverse effects. Drugs, such as ETH, that are effective in controlling absence seizures affect the T-type calcium currents. The most frequent adverse effects of ETH are gastric irritation. This can often be controlled by taking it after eating rather than on an empty stomach. Absence epilepsy is not effectively treated with phenytoin, gabapentin, or carbamazepine. Exacerbation of absence seizures following the administration of these ASDs has been shown.
5. The genetic epilepsies with generalized seizures should be viewed as a spectrum of conditions involving absence, myoclonic, and generalized seizures. The prognosis is usually very good for patients with absence seizures. Most will be controlled with ASDs. Spontaneous remission occurs frequently in patients with CAE. However, absence seizures may also persist into adulthood and will be accompanied by generalized tonic–clonic seizures or less frequently will evolve into other epilepsy syndromes with generalized seizures.

Clinical Pearls

1. Absence seizures can be detected in the outpatient setting during routine EEG. When the typical staring spell is accompanied by a burst of 3 Hz GSW, a typical absence seizure can be diagnosed. Absence may be precipitated by hyperventilation. An EEG is diagnostic in over 90 % of untreated patients with childhood absence epilepsy.

2. Staring spells are very common complaints of childhood. They may be differentiated by EEG. The 3 Hz GSW pattern is the typical feature of CAE. Focal seizures have focal epileptiform activity during seizures, while non-epileptic inattention (daydreaming) has a normal or a drowsy EEG pattern that is present. When in doubt, video-EEG monitoring is beneficial for diagnosis when the habitual event is captured.
3. ETH is the drug of choice for patients with CAE. When accompanied by other seizure types such as myoclonic seizures or generalized seizures, the ASDs such as valproate and lamotrigine should be considered.
4. The response to AED treatment may be addressed with EEG. Effective therapy will eliminate prolonged bursts of 3 Hz GSW discharges with clinical signs that suggest seizures associated with epileptiform discharges.
5. The prognosis of CAE is typically good, with absence seizures being readily treatable in the majority of patients. Up to 50 % of patients will remit in early adolescence, while some may develop other generalized seizure types such as myoclonus or GTC seizures, which require long-term therapy.

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Chapter 5
Lennox–Gastaut Syndrome

William O. Tatum IV

Case Presentation

A 28-year-old mentally retarded male resident of a group home had a documented medical history indicating that he had "shakes" when he was 12 months old that required "shots." His charted information identified a past medical history of frequent spells during his childhood that responded to "steroids" and eventually ceased. His development had been normal after the "spells"; however, he had a notable loss of cognitive function and was severely delayed in his development. He was diagnosed with epilepsy after developing episodes where he would "become rigid" and abruptly fall to the ground, which often resulted in injury. Sometimes there would be a sudden jerk prompting him to drop to the floor. "Grand mal" seizures became prominent. He also developed daily episodes of staring. He was brought for an opinion regarding treatment by his group home managers and was diagnosed with epilepsy that quickly became resistant to multiple ASDs. The ketogenic diet was instituted, but he was unable to maintain compliance with the food restrictions. Seizures and "pseudoseizures" were reported based upon bizarre "behaviors" and jerking that would occur despite being fully conscious. This prompted his group

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W.O. Tatum et al. (eds.), *Epilepsy Case Studies: Pearls for Patient Care*,
DOI 10.1007/978-3-319-01366-4_5,

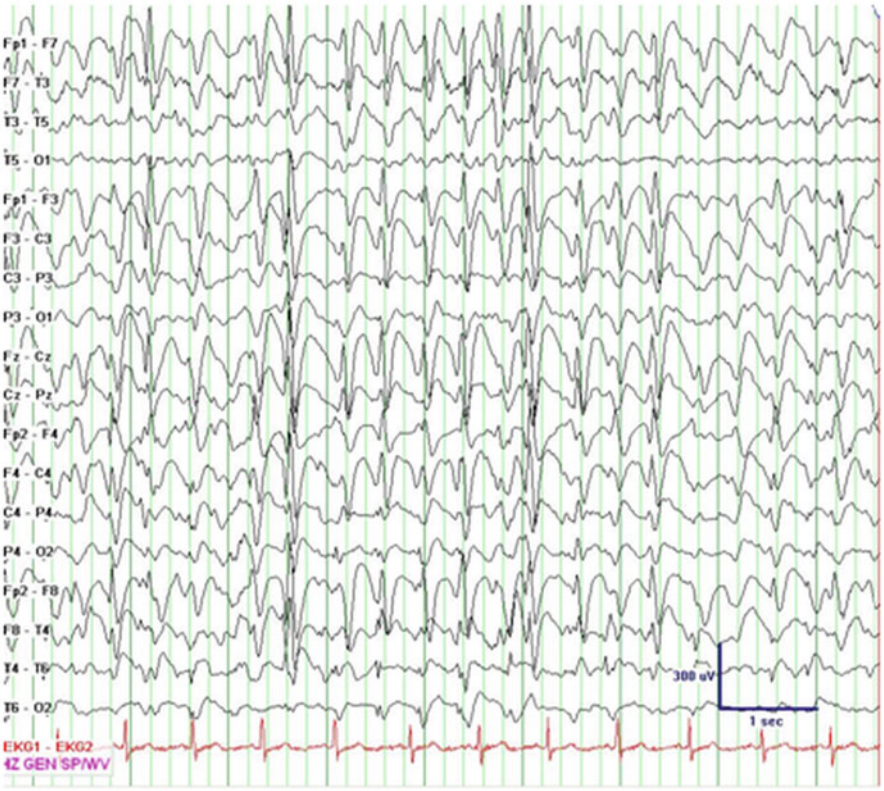

Fig. 5.1 Interictal EEG demonstrating a run of generalized bifrontally predominant 2–2.5 Hz slow-spike-and-wave discharges

home to introduce behavioral modification techniques with "time-outs" and food deprivation. MRI demonstrated mild atrophy. A routine EEG (Fig. 5.1) revealed the following:

Clinical Questions

1. How does the EEG help support the clinical history for a diagnosis?
2. What should the family know about this condition?
3. What other conditions may mimic this case presentation?
4. What is the best course of treatment?
5. What is the anticipated prognosis?

Diagnostic Discussion

1. The EEG demonstrates generalized slow-spike-waves. This is one of the characteristic features of the electroclinical syndrome of LGS. Other common features on the EEG include diffuse slowing of the background activity, the presence of multifocal independent epileptiform discharges, and bursts of generalized paroxysmal fast activity (GPFA).
2. The family must be made aware of the diagnosis with attendant EEG features, mental retardation, and the presence of multiple mixed seizure types. The anticipated poor seizure control, lack of singular etiology, and the potential for injury—despite treatment—should be discussed. It is important for the family to have reasonable expectations of seizure reduction and be provided with rescue therapies (i.e., diazepam rectal gel) in the case of serial ("cluster") seizures. They should understand that they do not need to go to the emergency department (ED) with every seizure, but that injury, persistent seizures, cardiorespiratory compromise, and failure to recover after a seizure should direct physician assessment. Seizure counts to quantify the number of different seizure types are a helpful attempt to reflect the degree of changes in seizure frequency. Epileptic spasms (West's syndrome) may precede LGS with adrenocorticotropic hormone (ACTH) "shots" in 40 %. Measures to protect the patient from falls and injury should be a primary focus to optimize safety. Quality of life should balance the effect of intermittent seizures with the presence of constant side effects of treatment.
3. Many encephalopathic generalized epilepsies may appear to have uncontrolled seizures from many different etiologies. LGS is considered a distinctive electroclinical syndrome based upon the following criteria:

   (a) Multiple mixed seizure types including tonic, atonic, tonic–clonic, atypical absence, and focal seizures.
   (b) The presence of mental retardation or evidence of cognitive impairment.
   (c) Slow-spike-waves with or without GPFA that are present on the EEG.

   The causes of LGS in many cases are unknown. However, reversible etiologies such as hydrocephaly, endocrinology, metabolism, and drug-related changes in association with compromised mental function and seizures should be investigated.
4. The best course of treatment is to use broad-spectrum ASDs. ASDs that have proven useful in clinical trials include lamotrigine (LTG), topiramate (TPM), rufinamide (RUF), and clobazam (CLB). Felbamate is useful, although its use is limited due to serious side effects, including aplastic anemia and liver failure. Valproate (VPA) is effective against multiple seizure types and may be helpful in combination with TPM or LTG; however, combination with LTG may cause a higher risk of serious rash however. RUF and CLB are more recently approved treatments that may be useful in the treatment of LGS. Levetiracetam and zonisamide are broad-spectrum ASDs that may also be considered. Dual ASDs are often used given the predisposition for frequent seizures and status epilepticus. The ketogenic diet and vagus nerve stimulation may also help. Finally, corpus callostomy is reserved for those with disabling injurious drop attacks.

5. The clinical course for patients with LGS typically carries a poor prognosis.
   Disability due to epileptic seizures and comorbid mental retardation and behavioral disorders predispose the patient with LGS to multiple recurrent injuries and a sheltered supervised environment.

Clinical Pearls

1. LGS often follows epileptic spasms that are caused by West's syndrome in early childhood through adulthood. The clinical triad of mental retardation, drug-resistant mixed seizure types (especially tonic seizures), and slow-spike-waves on the EEG characterize the syndrome.
2. There is a limited expectation that patients with LGS will achieve seizure control. Therefore, the focus of treatment should be to attempt to balance seizure reduction with an effort to minimize side effects from ASDs to promote an optimal individualized quality of life.
3. Reversible structural lesions are seen infrequently. Rather, diffuse injury or congenital malformation of the brain is oftentimes responsible. Intermittent exacerbation during periods of seizure control and alteration in mental status and behavior due to systemic or "toxic" effects from medication are common and require vigilance to resolve the iatrogenic contributing factor in clinical deterioration.
4. LTG and VPA or LTG and TPM are combinations that may be synergistic in the treatment of the LGS. VNS may be a useful adjunct when AED adverse effects are prominent. Vagus nerve stimulation may be helpful to minimize multiple drug exposure and reduce seizures. Corpus callosotomy for disabling injurious drop attacks is best performed at experienced centers.
5. Protection includes safe-guarding the home, head gear during "at-risk" times, and evaluation for significant medical care requiring ED visitation (e.g., status epilepticus). The overall prognosis for seizure control is poor and the expectation is unfortunately lifelong.

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Chapter 6
Benign Childhood Epilepsy with Centrotemporal Spikes

David N. Hammond

Case Presentation

An 8-year-old boy presents with recurrent spells that occur during sleep. They are most commonly noted shortly after he falls asleep. His parents observe unilateral facial twitching and drooling, and hear him make "gurgling" sounds. He appears to be awake during the spell, but is unable to speak. The spell occurs for approximately 1 or 2 min. Afterwards, he takes a couple of minutes to recover but is able to recall the event. He reports a sensation of numbness that will affect his lips and tongue that are present on the same side as the facial twitching. Because of the disruptive nature of the spells, the family is seeking medical attention for diagnosis and treatment. The patient is otherwise healthy and engaged in activities at home and at school. His development has been normal. The neurologic and general examinations are also normal. Laboratory studies are unremarkable, and a sleep-deprived electroencephalogram (EEG) is ordered (Fig. 6.1).

Clinical Questions

1. How does this EEG support a particular clinical diagnosis?
2. What is the prognostic significance of centrotemporal spikes?
3. What are pediatric focal epilepsy syndromes, and what characteristics do they share?
4. Do patients with benign epilepsy with centrotemporal spikes (BECTS) require medication?
5. What is the anticipated clinical course and prognosis in BECTS?

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W.O. Tatum et al. (eds.), *Epilepsy Case Studies: Pearls for Patient Care*,
DOI 10.1007/978-3-319-01366-4_6,

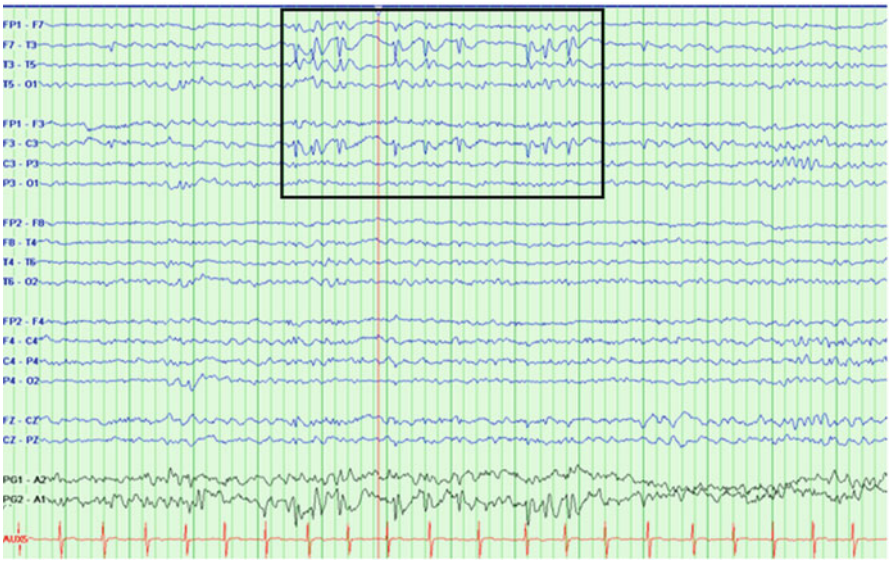

Fig. 6.1 EEG shows pathological epilpetiform spikes (*box*) in the left centrotemporal region

Diagnostic Discussion

1. Spikes and sharp waves followed by aftergoing slow waves emanating from the centrotemporal region, typically with a negative maximum at the C3 + T7 and/or C4 + T8 electrodes, and with frontal positivity, are classically seen in BECTS. BECTS is the most common of the pediatric focal epilepsy syndromes. The interictal epileptiform activity can occur either unilaterally (approximately 60 % of cases) or bilaterally (approximately 40 % of cases). Spikes can occur during wakefulness, but are more prominent during non-REM sleep when they can occur very frequently, seemingly out of proportion to the clinical seizure history.
2. The frequency of the centrotemporal spikes does not correlate well with the frequency or the duration of seizures in a patient with BECTS. Indeed, interictal spikes on EEG may persist long after resolution of the clinical seizures and, hence, do not aid in deciding when to discontinue an antiepileptic drug (AED). Furthermore, many children with centrotemporal spikes never develop clinical seizures.
3. BECTS, as noted above, is the most common of the three focal epilepsy syndromes recognized by the International League Against Epilepsy (ILAE). It accounts for 10–20 % of the new-onset pediatric epilepsies. The other two common focal epilepsies are early-onset childhood occipital epilepsy (Panayiotopoulos type) and late-onset childhood occipital epilepsy (Gastaut type). These three syndromes share several features. A genetic predisposition has been noted; however,

various genetic and environmental factors influence the clinical phenotype. There is also a developmental age-specific onset of symptoms, with BECTS seizure onset peaking at 7–10 years of age. Lastly, the clinical course is marked by relatively mild seizures, amenable to AED treatment, which spontaneously remit (see below).

4. Not all patients with BECTS require treatment with an AED. When brief focal seizures (see below) occur infrequently, the parents and physician may opt not to treat with an AED and to incur the risk of chronic AED therapy. Levetiracetam, oxcarbazepine, and other non-sedating ASDs have been used for those patients requiring treatment.
5. Despite the focal EEG abnormalities, brain MRI scans do not demonstrate any significant abnormality. Children typically demonstrate normal development. However, some manifest mild neuropsychological abnormalities and academic difficulties. Focal seizures may evolve to include convulsive seizures. Clinical remission may occur 2 to 4 years after onset, though typically before 16 years of age. It is very unusual (<1 %) for BECTS to evolve to a more severe epilepsy with drug-resistant seizures.

Clinical Pearls

1. BECTS is the most common pediatric localization-related epilepsy syndrome, typically presenting in an age-dependent fashion with sleep-activated focal seizures.
2. While there is a genetic predisposition, other genetic and environmental factors likely play a role in determining whether or not seizures will occur.
3. The typical findings of frequent interictal centrotemporal epileptiform abnormalities present during sleep on EEG support the diagnosis of “rolandic” epilepsy.
4. The prognosis is excellent. There are in general terms seizures that occur that are relatively mild composed of focal seizures without convulsions. Additionally, the seizures are amenable to AED treatment (if needed), and spontaneously resolve in adolescence.

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Chapter 7
Juvenile Myoclonic Epilepsy

William O. Tatum IV

Case Presentation

A 21-year-old right-handed white female with well-controlled epilepsy developed normally without medical conditions or risk factors. Seizure onset was noted at 17 years of age after a night of "cramming" for a final examination in history class. After the test she stayed out with friends until 1 AM. She admitted to drinking four Red Bull® energy drinks and staying out late with friends before returning home to sleep. The following day she experienced headache and nausea. When she went to brush her teeth, her right arm jerked, and her toothbrush was jettisoned from her hand. She went to eat breakfast but continued to be "shaky" and found it difficult to eat her cereal due to jerky motions that created trouble guiding the spoon to her mouth. She then described the occurrence of similar jerking in the morning in the first half hour of awakening over the last 2 years. As she was telling her parents about the night before, she suddenly turned her head to the left, let out a scream, and fell to the ground. She was unconsciousness and manifested generalized tonic stiffness and clonic jerking bilaterally for 1 min. She was then tired, sleepy, and confused. Her parents called 911, and she was taken to the ED. In the ED, she was disoriented and confused but without focal or lateralizing features to her neurological examination. A CT brain was normal. An EKG and laboratory testing included a normal CBC, liver function studies, and electrolyte panel, and creatinine was normal. She was given intravenous levetiracetam and was admitted to the hospital overnight. An MRI of the brain was normal and an EEG had the following results (see Fig. 7.1).

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W.O. Tatum et al. (eds.), *Epilepsy Case Studies: Pearls for Patient Care*,
DOI 10.1007/978-3-319-01366-4_7,

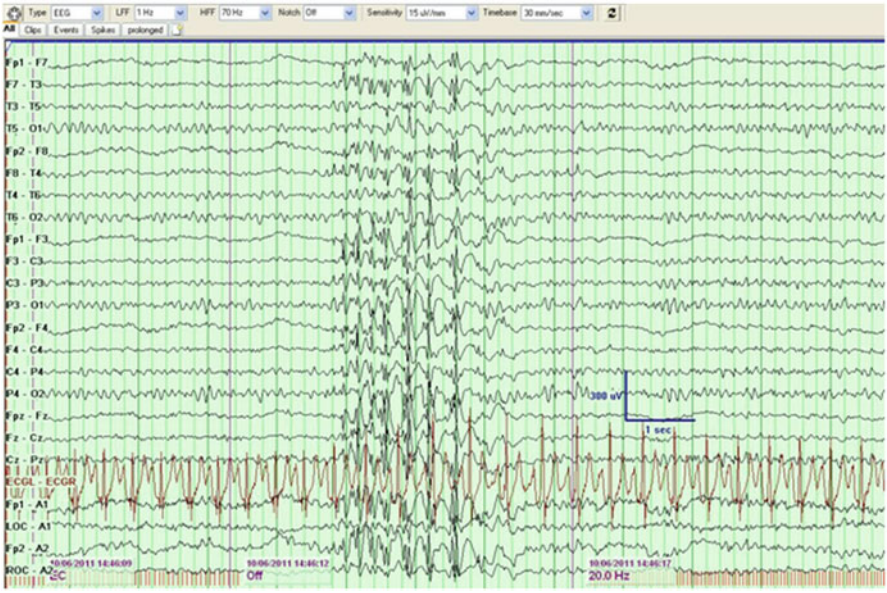

Fig. 7.1 Generalized spike- and polyspike-and-waves with a repetition rate of 4–5 Hz at the onset of a 2-s burst of interictal epileptiform activity that occurred without clinical signs

Clinical Questions

1. Does this patient have epilepsy?
2. What would you expect the EEG to demonstrate?
3. What clinical features characterize this epilepsy syndrome?
4. What is the best treatment for this condition?
5. What is the prognosis for this patient?

Diagnostic Discussion

1. Our patient had only a single generalized tonic-clonic seizure; however, generalized upper-body predominant single lightening-like jerks that occur in the morning and result in spilling drinks or throwing objects such as a toothbrush represent myoclonic seizures. These are brief shock-like jerks that involve the shoulders, face, arms, and legs and may precede the onset of convulsions by 2 years. They appeared in our patient at 15 years of age, the peak age of onset. The clinical presentation of juvenile myoclonic epilepsy (JME) is an initial GTC seizure that occurs in otherwise healthy individuals the morning after a night of sleep deprivation and/or alcohol consumption. The peak age of onset is typically 12–18 years of age. In this case, the seizures were precipitated by sleep deprivation and

the use of energy drinks. Sleep deprivation, alcohol, stimulant drugs, strobe lights or video games, and energy drinks may all act as precipitating factors.

2. EEG supports a clinical diagnosis of epilepsy. In this case, an interictal EEG demonstrated generalized spike- and polyspike-and-wave at >3 Hz. The interictal EEG is abnormal in 50–85 % of untreated patients with JME. The characteristic electrographic feature includes "fast" 3–5 Hz generalized bilateral frontocentral predominant, symmetric synchronous polyspike-and-waves as in the case above. Photosensitivity seen with photic stimulation occurs in 30–50 % of patients stimulated at midrange frequencies (about 15 Hz). This supports a generalized mechanism in a patient with a clinical diagnosis of seizures. The polyspike formation is suggestive of myoclonic seizures.
3. JME is the most common form of genetic generalized epilepsies and the most common cause of primary GTC seizures. It is characterized by adolescent-onset myoclonic jerks that occur with morning predominance. Generalized tonic-clonic seizures are seen in 95 % of patients who are ultimately diagnosed with epilepsy. Many of these are described as clonic-tonic-clonic seizures due to the crescendo myoclonus that ultimately culminates in a GTC seizure. Up to 50 % may have subtle lateralizing signs either in the clinical semiology or on the EEG. Absence seizures are less commonly encountered in JME and affect approximately 1/3 of patients. Yet, it is the myoclonus and generalized seizures that are the signature of this syndrome. JME may be elusive until convulsions are recognized. MRI brain is typically normal. Evidence of frontal dysfunction has been postulated as the underpinning for this genetic generalized epilepsy syndrome. The genetic component of JME is likely complex and polygenetic, and about 40 % of JME patients report a family history of epilepsy.
4. Patients with JME should receive treatment with antiseizure drugs. Even though our patient had only a solitary GTC seizure, the myoclonic seizures and JME syndrome imply recurrence if left untreated. Broad-spectrum drugs such as valproate, lamotrigine, and levetiracetam are useful ASDs. Topiramate and zonisamde may also be used in place of the enzyme-inducing ASDs, which can be sedating in the case of barbiturates, or can exacerbate generalized seizures in the case of carbamazepine, phenytoin, and gabapentin. Special considerations are required when treating women of childbearing age. While all the ASDs have a risk for birth defects, valproate has the highest teratogenic risk and should be avoided in young females due to major congenital malformations and cognitive dysfunction that is evident during early childhood development. In males, valproate is an effective choice due to its efficacy in treating the multiple seizure types associated with JME.
5. Most patients with JME do very well and are easily controlled with the correct medication. While control is usually obtained through AED treatment, breakthrough seizures may occur from noncompliance. Lifestyle changes are very important with the need to observe regular sleeping habits, avoid drugs and alcohol, and remain compliant with antiseizure medication. Treatment is usually rendered for life given the high percent that relapse will occur if ASDs are withdrawn. Still, approximately 15 % of cases are drug resistant and require additional treat-

ments which may include the vagus nerve stimulator or modified Atkins diet. Epilepsy surgery is not indicated for JME.

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Chapter 8
Focal Seizures in Children

Katherine Nickels

Case Presentation

A 13-year-old right-handed boy has been healthy until 1 year ago when he developed the onset of recurrent "spells." He comes for an evaluation with his parents who report that the spells have all looked the same when witnessed. He will initially feel a warning of a sudden "funny feeling" and have difficulty understanding what is being said. He is then seen to stare, be unresponsive to questioning, exhibit a behavioral arrest, and develop heavy breathing. The entire event lasts for less than a minute and afterwards his speech is altered. His parents notice that while his words are easily understood, there are prominent word substitutions and new words that do not make sense. He had a normal birth, labor, and delivery without perinatal complications, and his development was normal. There were no risk factors for epilepsy, including febrile seizures, meningitis or encephalitis, or head trauma. Additionally, there was no family history of seizures. Over the last year there has been a mild decline in his grades reflected by a slow deterioration in his test scores. His neurological examination was normal. A brain MRI was without abnormality. An EEG was obtained and demonstrated the following (see Fig. 8.1):

Clinical Questions

1. What do these "spells" likely represent?
2. Based on the behavior, which region(s) of the brain might be involved?
3. How is a diagnosis of seizures supported by the EEG?
4. What is the likely etiology for these events?
5. What is the prognosis for this child?

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W.O. Tatum et al. (eds.), *Epilepsy Case Studies: Pearls for Patient Care*,
DOI 10.1007/978-3-319-01366-4_8,

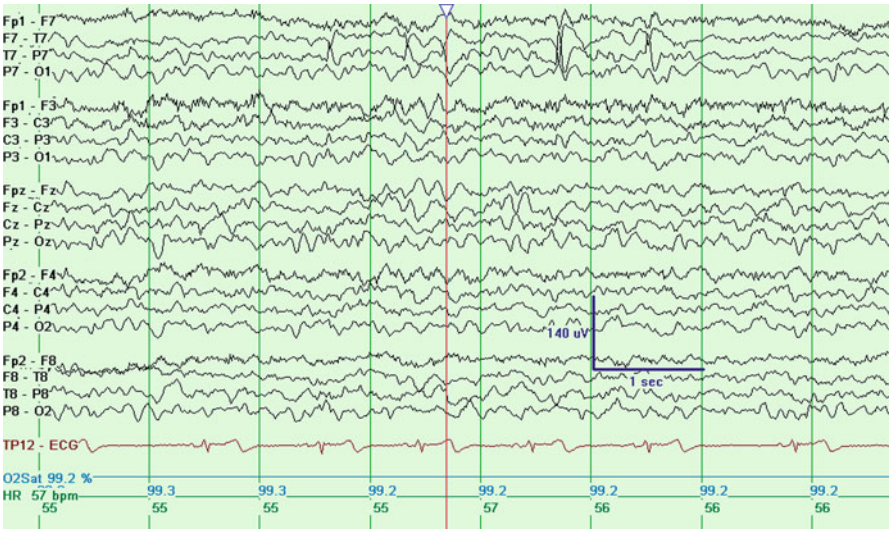

Fig. 8.1 Interictal routine scalp EEG demonstrating frequent T7 sharp waves with a regional temporal field

Diagnostic Discussion

1. These spells likely represent focal seizures. Seizures are a common neurological condition in children that are paroxysmal, and repetitive, demonstrating a stereotyped semiology with impaired consciousness to distinguish them. However, there are other possible etiologies. The "funny feeling" could be related to cerebral hypotension from neutrally mediated syncope, but the unresponsiveness with retained posture and consciousness is atypical. The strange feeling might reflect anxiety-associated hyperventilation interpreted as "heavy breathing," though the brevity of the event and the unresponsive state make this unlikely. Finally, distractibility, amnesia, and aphasia have rarely been reported as part of migraine aura, yet in this case, headache and constellation of migraine including nausea and vomiting, photo- or phonosensitivity, and a protracted course were absent.
2. A language dysfunction is noted with the event. Because the patient is a right-handed individual, you would expect the left hemisphere of the brain to be language dominant. The difficulty understanding what is being said reflects a posterior (receptive) aphasia which occurs as an aura. Post-ictally, there are paraphasic errors noted, also suggesting language involvement. Postictal aphasia has a 90 % positive predictive value for being associated with the dominant hemisphere. Furthermore, the semiology manifests as staring and evolves to include a brief behavioral arrest, which is commonly associated with temporal lobe involvement. The first symptom of a "funny feeling" may suggest a psychic or experiential aura

which is often seen with involvement of the mesial temporal structures. Therefore, the clinical localization suggests a left temporal localization.
3. The EEG demonstrates frequent epileptiform discharges in the left temporal electrode region. This is congruent with the clinical lateralization and anticipated localization of seizure onset and provides strong support for an epileptogenic etiology for the patient's "spells." More than 90 % of patients with anterior temporal epileptiform discharges will have focal seizures.
4. This child has a normal neurologic exam, normal MRI (performed with epilepsy protocol), and no family history. Therefore, with no risk factors for epilepsy, the etiology of this child's epilepsy is unknown. Previously, this would be labeled as "cryptogenic," but the report of the ILAE Commission on Classification and Terminology, 2005–2009, has recently reclassified this as an "unknown cause." Other unidentified causes, such as a malformation of cortical development that is too small to be seen on neuroimaging, cannot be excluded.
5. The prognosis for children with focal epilepsy of unknown etiology is typically favorable when compared to symptomatic localization-related epilepsy where focal seizures are caused by a structural (aka structural-metabolic) cause. In a long-term population-based study, only 7 % of children with focal epilepsy due to unknown etiology were intractable, while 81 % were seizure free. Of those who were seizure free, 68 % were ultimately able to discontinue antiseizure medications. For those children with temporal lobe epilepsy of unknown etiology who are refractory to medications, temporal resection should be considered and is often helpful to render the patient seizure free. In patients with temporal lobe epilepsy, but with a normal MRI, concordance of the presurgical evaluation also results in favorable postsurgical outcomes. Patients with focal temporal PET hypometabolism and congruent "phase 1" evaluations with scalp video-EEG localization have been shown to have a favorable seizure-free result following anterior temporal lobectomy, which may be similar to those with mesial temporal sclerosis on brain MRI.

Clinical Pearls

1. The ictal behavior of an event forms the basis for a clinical diagnosis of a seizure. Lateralizing signs such as peri-ictal aphasia are important in providing a clinical localization in patients with focal seizures. Most children exhibit semiologies that parallel adult seizures by the time they reach 6 years of age.
2. Children with focal seizure features during their seizure and those with focal EEG abnormalities should undergo a brain MRI. High-resolution brain MRIs with a dedicated seizure protocol provide the highest yield. If a child has seizures with normal neuroimaging, normal learning and development, and a normal neurological examination, then the likelihood of a gross underlying structural basis is relatively low compared to those with an unknown cause.
3. EEG remains the test that is most specific for a clinical diagnosis of epilepsy. The interictal EEG may provide a clue to differentiating paroxysmal "spells." An

ictal EEG is diagnostic when the typical event is recorded to provide additional lateralizing and localizing information for the purposes of treatment.

4. Children with localization-related epilepsy and focal seizures that occur without a known etiology are more likely to have normal cognition, have a normal neurological examination, and be medication responsive. These children are also more likely to be able to successfully discontinue ASDs when they remain seizure free following treatment.
5. Children with focal temporal hypometabolism on FDG-PET scans yet have a normal brain MRI and drug-resistant seizures will have a similar outcome following anterior temporal lobectomy as those with hippocampal sclerosis.

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Chapter 9
Generalized Epilepsy with Febrile Seizures Plus

William O. Tatum IV

Case Presentation

A 15-year-old girl was born the second of three children with a normal birth, maternal labor, delivery, and development. Ear infections were recurrent as a child. At 1 year of age she experienced a convulsion during a fever of 102.7 °F. The seizures were noted to occur with an abrupt onset and sudden generalized stiffening of the body and extremities. A loss of consciousness occurred with rhythmic body clonic jerking. At the hospital she was diagnosed with a febrile seizure (FS). She would develop generalized tonic–clonic seizures when febrile intermittently over the years continuing until she was 9 years old when afebrile seizures were noted. She experienced recurrent FS during fevers due to recurrent ear infections. Her mother, sister, and grandmother also experienced FS. Initially, a CT of the brain and a lumbar puncture were normal. Later an EEG was normal. At first, she was given a prescription for diazepam rectal gel in case of a prolonged seizure recurrence. With recurrences that persisted, she was begun on carbamazepine. With carbamazepine a second type of seizure became noted, characterized by single body jerk that would lead to brief stiffening with "head nods." A pediatric epileptologist was consulted after a focal seizure. Brain MRI was normal (Fig. 9.1a), and EEG (Fig. 9.1b) had a normal background with generalized spike- and polyspike-and-waves. AED change to valproate led to seizure control. At 12 years old she was then changed to levetiracetam, which has maintained seizure freedom.

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W.O. Tatum et al. (eds.), *Epilepsy Case Studies: Pearls for Patient Care*,
DOI 10.1007/978-3-319-01366-4_9,

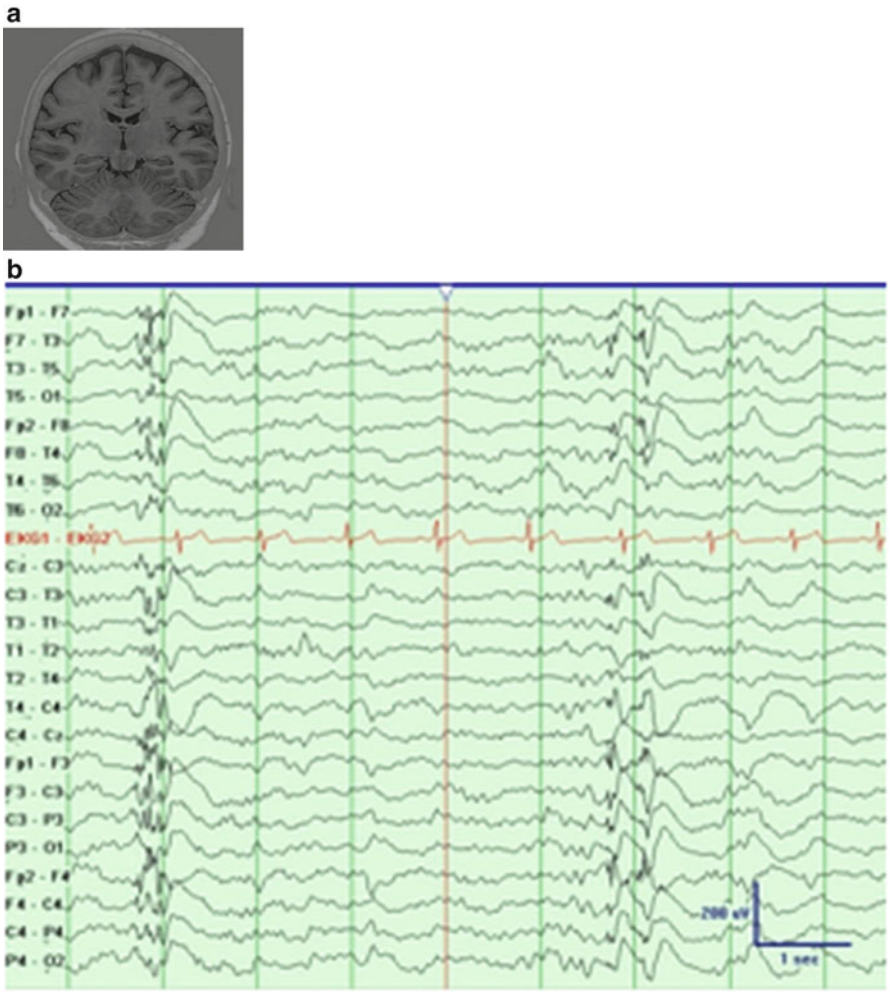

Fig. 9.1 (**a**) Normal coronal brain MRI and (**b**) EEG demonstrating a single generalized polyspike-and-wave in second 2 and generalized spike-and-waves in second 7

Clinical Questions

1. How often are febrile seizures inherited?
2. What are the epilepsy syndromes that may result?
3. What does the evaluation suggest in this patient?
4. What is the role of ancillary testing in the diagnosis?

5. What is the anticipated clinical course and prognosis?

Diagnostic Discussion

1. Involvement of several family members suggests an inherited pattern. However, a single mode of inheritance has not been established for FS. However, FS occur with approximately a two- to threefold prevalence among the family members of affected children when compared with a similar normal population. If the parents are affected, this increases the risk that FS will occur in their offspring. In addition the risk is increased when both parents are affected and it predicts a greater likelihood of recurrent FS. Asian families in particular are at risk for FS and have demonstrated a population effect. Overall approximately one-third of FS will recur and be more likely if the age of onset is less than 1 year. Most are simple FS without a significance risk for subsequent epilepsy. However, in 10–20 % of children complex FS and febrile status epilepticus may occur and carry a greater risk of chronic epilepsy especially if there is a prolonged fever, family history, or presence of a neurological deficit.
2. The types of epilepsy that may result include focal and generalized seizures. A minority of patients with FS develop afebrile seizures and those with complex FS account for the majority. The association with prolonged FS and temporal lobe epilepsy due to hippocampal sclerosis (often drug resistant) is known though it remains controversial. Temporal lobe seizures are more likely to remit if a first-degree relative has had an FS. Other generalized seizure types include generalized tonic–clonic with and without absence seizures. Localization-related epilepsy (TLE), hemiconvulsion-hemiplegia-epilepsy (HHE syndrome), with severe febrile status occurs with recurrent focal seizures. Generalized epilepsy with a genetic component (i.e., Doose syndrome and myoclonic absence epilepsy) in addition to generalized epilepsy with febrile seizures plus (GEF+) may also occur. In this case, a normal mental status makes a malignant epileptic encephalopathy unlikely (i.e., Dravet's syndrome).
3. The presence of recurrent FS beginning in early childhood that persists beyond the age of 6 years old (the normal cutoff for FS) in addition to the prominent family history and heterogeneous generalized seizures suggests GEF+. This syndrome may be more common than was previously known. The family history of FS is the key to the clinical diagnosis. Tonic, myoclonic, atonic, absence, and focal seizures may occur and persist into adolescence or adulthood. The brain MRI and the neurological examination are normal though cognitive impairment may occur. EEG ranges from normal to demonstrating interictal epileptiform discharges.
4. Genetic factors are increasing in their importance relative to both diagnosis and treatment of epilepsy. An autosomal dominant mode of inheritance with incomplete penetrance has been demonstrated in GEF+. Multiple FS gene mutations with different loci have been identified including several mutations that involve

the sodium channel and GABA-A receptor subunit. Sodium channel dysfunction of sodium channel inactivation (SCN1A) may result in hyperexcitability. Sodium gating modulation by SCN2A may lead to interference with the voltage-gated beta subunit encoding. A reduction in the inhibitory effect by a mutation in a subunit of the GABA-A receptor (GABRG2) may interfere with benzodiazepine binding. SCN2A has also been associated with GEF+. Various subtypes of GEF+ have been identified based upon the gene mutation involved making diagnosis easier with genetic analysis. The EEG of GEF+ may be normal as it was in this case. On EEG interictal epileptiform discharges showed irregular generalized spike- and polyspike-and-waves with a repetition rate of 2.5 Hz supporting a clinical diagnosis of generalized epilepsy. Focal spikes may also be present in the EEG of patients with GEF+.

5. Classification systems use terminology and concepts of seizure onset to organize knowledge of the types of epilepsy and predict the clinical course and response to treatment. Definitions to distinguish focal and generalized seizures have been recently revised without utilizing EEG. In this case, "pseudo-resistance" to carbamazepine occurred from misclassification of the epilepsy as localization related. The treatment course was complicated when seizures were not controlled due to the sodium channel-blocking mechanism that is operational with carbamazepine. Generalized (genetic) epilepsy syndromes such as GEF+ may not respond to narrow-spectrum ASDs used to treat focal seizures and even provoke new types of seizures (tonic/myoclonic seizures) as in this case. AED substitution with valproate as a mixed function Gaba-ergic drug leads to complete control of all seizures stressing the importance of EEG and genetics in diagnosis and treatment as noted in our patient with GEF+ and a mutation of the sodium ion channel.

The prognosis is typically favorable and is phenotypically based. Remission may occur in early adolescence though if phenotypes characteristic of other epilepsy syndromes that uncharacteristically remit (i.e., JME, Doose syndrome, or localization-related epilepsy) then seizures may persist.

Clinical Pearls

1. Febrile seizures are the most common seizures seen in early childhood, involving various modes of inheritance with a <5 % likelihood of developing epilepsy.
2. While complex FS associated with hippocampal sclerosis is well known to exist in patients with temporal lobe epilepsy, generalized seizures may also be associated with FS.
3. GEF+ is a hereditary epilepsy syndrome associated with febrile seizures. It reflects an autosomal dominant mode of inheritance with a clinical course of persistent FS beyond age 6 years evolving into an afebrile heterogeneous group of generalized seizures.

4. Interictal epileptiform abnormalities on EEG may support the clinical diagnosis of generalized epilepsy, though serological testing for SCN1A, SCN1B, and GABRG2 may provide genetic confirmation of the diagnosis.
5. The treatment should avoid sodium channel-blocking agents, which may exacerbate seizures. The prognosis of GEF+ is usually favorable with seizure control and the potential for spontaneous resolution in adolescence.

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Chapter 10
Comorbidity and Seizures

Matthew T. Hoerth

Case Presentation

A 21-year-old right-handed Caucasian female began to have worsening depressive symptoms, and later developed nausea and headache 2 months prior to presentation. Upon presentation to the clinic for evaluation, her family reported that she had begun to experience language difficulties, memory disturbance, and auditory hallucinations. Emergency medical personnel were notified after the patient experienced a nocturnal generalized tonic–clonic seizure. During the first several days after admission, she was agitated with stereotyped episodes of stiffening and head jerking, recognized to be seizures, and antiepileptic medication was initiated. Despite this, the patient continued to have frequent seizures during the hospitalization, which culminated in nonconvulsive status epilepticus, confirmed by EEG. The patient was intubated and placed on a continuous infusion of several antiepileptic medications. For days, different combinations of antiepileptic medications were tried, but she continued to remain in status epilepticus. An MRI of the brain, routine laboratory, and urine drug screen were normal. She was healthy otherwise without any known seizure risk factors. There was no exposure to other drugs or toxins, as well as no sign of systemic or central nervous system infection. She ultimately underwent a lumbar puncture in an effort to determine the etiology for her nonconvulsive status epilepticus. The results are shown in Table 10.1.

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W.O. Tatum et al. (eds.), *Epilepsy Case Studies: Pearls for Patient Care*,
DOI 10.1007/978-3-319-01366-4_10, © Springer Science+Business Media New York 2014

Table 10.1 Cerebrospinal fluid profile obtained during nonconvulsive status epilepticus

CSF fluid analysis	Result
Appearance	Clear
Color	Colorless
Glucose	66
Protein	31
RBC	18.0 H
Nucleated cells	16.5 H
Lymph	88 % H
Mono	12 % L
Oligoclonal bands	10
IgG index	2.60 H
IgG/albumin ratio	0.65 H
Synthesis rate	24.90 H
Blastomyces antibody	Neg
Cryptococcus antigen	Neg
Histoplasma antibody	Neg
VDRL	Neg
Lyme	Neg
West nile virus IgG, IgM	Neg
Enterovirus PCR	Neg
HIV antibody eval	Neg
Varicella zoster virus PCR	Neg
Herpes simplex-1 PCR	Neg
Herpes simplex-2 PCR	Neg
CMV PCR	Neg
Parovirus B19 PCR	Neg
Angiotensin-converting enzyme	Neg
GAD65 antibody	0.00
ANNA-1	Neg
ANNA-2	Neg
ANNA-3	Neg
Amphiphysin antibody	Neg
CRMP-5	Neg
Neuronal VGKC antibody	Neg
Thyroperoxidase antibody	0.8 (nml <9.0)
Purkinje cell antibody	Neg
Anti-NMDA receptor antibody	Positive

Clinical Questions

1. What is the clinical significance of the elevated antibody titer and other CSF results?
2. What neoplasms, if any, are associated with anti-NMDA receptor antibody positivity?
3. Are there any potential alternatives to medications in prolonged status epilepticus?

4. Is there any role for immunosuppressant medications in anti-NMDA receptor antibody positivity?
5. What is the prognosis for this patient in anti-NMDA receptor antibody encephalitis?

Diagnostic Discussion

1. The presence of the anti-*N*-methyl-D-aspartate (NMDA) receptor antibody solidifies a diagnosis of autoimmune limbic encephalitis. Although multiple different autoantibodies have been implicated in refractory status epilepticus, the anti-NMDA receptor antibody was the first to be reported in 2007. This cell-surface antibody has been postulated to target epitopes on NMDA receptors located in the forebrain and hippocampus. This leads to the development of dyskinesias, autonomic instability, and seizures (often status epilepticus). Prodromal symptoms of headache, low-grade fever, and psychiatric symptoms (anxiety, agitation, hallucinations, paranoia) are often seen and should prompt clinicians to an autoimmune evaluation. The lymphocytic pleocytosis seen in this patient is often found in association with anti-NMDA receptor positivity (91 %); however, oligoclonal bands are only seen in a minority (26 %). Without the positivity of these antibodies, empiric autoimmune treatment could be tried, but aggressive immunosuppression in a critically ill patient would be empiric and risky.
2. Anti-NMDA receptor encephalitis is seen predominantly in females, although not exclusively (91 %). Tumors are seen in just over half of all patients (59 %). Almost all of them have been identified to be reproductive organ tumors (ovarian teratoma and teratoma of the testis), but small-cell lung cancer has also been reported. If a tumor is discovered, resection is the treatment of choice. This can reduce the antibody production and, in turn, the patient's symptoms. Persistence in searching for teratoma is required. It has been reported that not all ovarian teratomas are radiologically evident and exploratory laparoscopy has been required in some patients. Despite thorough investigation, no tumor was found in this patient.
3. Traditional antiepileptic medications are the mainstay for the initial treatment of status epilepticus. When status epilepticus is refractory to multiple medications, other alternatives should be considered. In this patient, the ketogenic diet was utilized with some degree of success in reducing continuous infusions of antiepileptic medications. There are a limited number of case reports describing the use of the ketogenic diet in refractory status epilepticus. In many of these limited cases, it has been shown to be beneficial. Obviously, care should be taken when altering the metabolism in a critically ill patient. In addition to the ketogenic diet, electroconvulsive therapy and vagus nerve stimulation have been described in case reports to have some benefit.
4. The potential benefit of immune-modulating therapy is to eliminate the antibodies that are operational in producing seizures and status epilepticus. Initiating treatment involves a costly evaluation and treatment for autoimmune causes. Appropriate guidelines for an evidence-based algorithm when considering

treatment of autoimmune limbic encephalitis have yet to be established. However, many centers use a similar approach. Without an identified tumor, first-line immunotherapy can consist of corticosteroids (usually high dose), intravenous immunoglobulin (IVIg), plasma exchange, or a combination. If these first-line methods are unsuccessful, then rituximab or cyclophosphamide is then considered. Currently, it is unclear whether chronic immunosuppressive agents are helpful in the prevention of relapses which can occur in 20–25 % of patients.

5. Prognosis in prolonged and refractory status epilepticus is typically poor. It has been suggested in animal models that the anti-NMDA receptor antibodies can cause neuronal dysfunction via inflammation. However, they cause less neuronal damage than other antibodies that may be found to produce autoimmune limbic encephalitis. In the original 100 patients described by Dalmau et al., 47 were noted to make a full recovery, and 28 people recovered with mild stable neurological deficits. This was despite a median length of hospitalization of 2.5 months. Early tumor identification and removal were found to be predictive of a better outcome. It should be noted that intrinsic to this series is a bias due to the ability to identify antibody positivity early so that tumor resection and/or immunomodulating treatment may be initiated.

Clinical Pearls

1. The ability to identify specific antibodies in autoimmune limbic encephalitis is relatively new in the evaluation of refractory status epilepticus.
2. When status epilepticus is refractory or superrefractory, then other treatment modalities, other than antiseizure drugs, should be considered. The ketogenic diet and other non-medication approaches show some promise.
3. Aside from antiepileptic medications, immune-modulating therapies should be considered if a case of autoimmune limbic encephalitis is identified. In many cases, success in patient outcome is a result of having a high clinical suspicion and the willingness to consider therapies other than standard antiepileptic medication.

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Chapter 11
Depression and Epilepsy

Kristine S. Ziemba

Case Presentation

A 32-year-old, right-handed gentleman with a long history of depression presents with a several-year history of brief paroxysmal recurrent spells of an unpleasant gastric sensation (as if his "stomach is turning around") and feeling of déjà vu. According to his wife, he will occasionally repeat phrases during the event such as "Oh, my stomach," and be unaware of the events after they occur. They suspect these events are happening about once or twice per week. He has never experienced a convulsion. The patient's only potential risk factor for seizures was a traumatic, closed-head injury and brief concussion that he sustained 12 years ago while serving in the military. He was ultimately dismissed from active military duty due to persistent depression, which was severe. He is currently maintained on paroxetine 40 mg daily with some improvement in mood, but admits to occasional passive suicidal ideation without an active plan. MRI of the brain and basic labs are within normal limits. He is admitted to the epilepsy monitoring unit (EMU) to clarify the differential diagnosis of the recurrent spells. Interictally, right temporal sharp waves were present. The following segment of EEG represents a clinical event that progressed to include bicycling motions of legs, mumbling, and inability to communicate (Fig. 11.1). The entire event lasted 1 min and 40 s. After the event the patient was amnestic for the episode that was identified by his family.

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W.O. Tatum et al. (eds.), *Epilepsy Case Studies: Pearls for Patient Care*,
DOI 10.1007/978-3-319-01366-4_11, © Springer Science+Business Media New York 2014

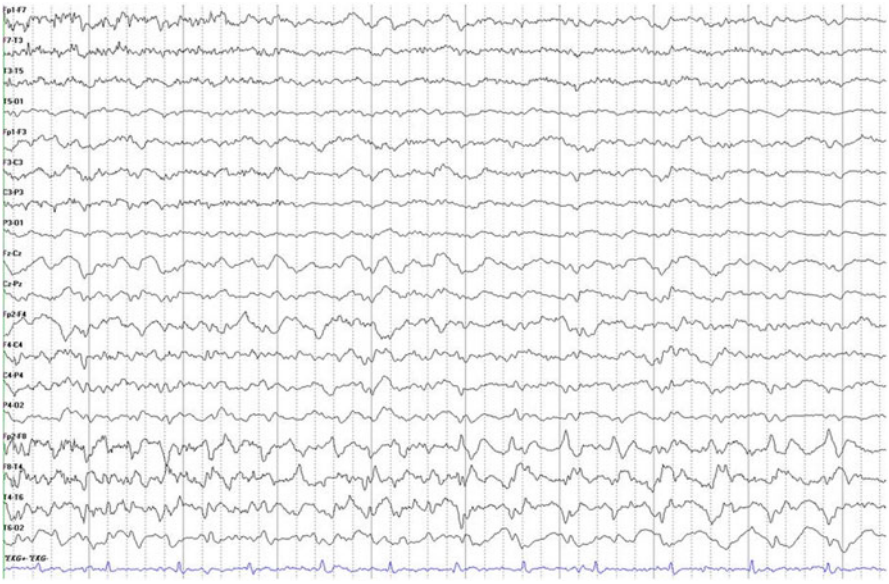

Fig. 11.1 EEG demonstrates an electrographic seizure that is maximal in the right anterior temporal region with a right hemispheric predominant bilateral field

Clinical Questions

1. Does this EEG support a particular clinical diagnosis?
2. What is the relationship between depression, epilepsy, and the risk of suicidality?
3. How does the patient's diagnosis of major depression impact your treatment plan (i.e., choice of AED)?
4. How would a diagnosis of epilepsy impact your recommendations for treatment for his depression?
5. What is the appropriate counseling for patients regarding epilepsy and comorbid depression?

Diagnostic Discussion

1. This EEG demonstrates rhythmic slowing of background activity over the right hemisphere, maximal in the right temporal region, which evolves in frequency and morphology to include sharp components. There is bi-frontal spread of the rhythmic slow waves. Although this is a single EEG "snapshot," it was able to confirm a seizure emanating from the right temporal head region that spreads to

involve both sides of the brain. In combination with the history and clinical picture, this is diagnostic of localization-related epilepsy, likely of right temporal lobe origin.

2. The lifetime prevalence of depression in people with epilepsy is approximately 30 %, which is significantly higher than for the general population. On average, the rate of death by suicide is ten times higher in people with epilepsy than in controls, and this increased risk is largely explained by the presence of comorbid depression. Recent studies have indicated a strong bidirectional association between epilepsy and depression with the presence of depression/suicidality frequently occurring both before seizures develop as well as after epilepsy has been diagnosed. Therefore, major depression puts one at higher than average risk for being diagnosed with epilepsy, and having epilepsy puts one at higher risk of being diagnosed with major depression. It is not only the case where the diagnosis and treatment of epilepsy *confer* a risk of depression (i.e., reactive depression). Rather, the relationship may reflect a common underlying pathophysiological mechanism that is common for both epilepsy and depression.
3. The presence of comorbid depression or other psychiatric comorbidity may lead you to consider an AED with mood stabilization properties, such as valproic acid, lamotrigine, or carbamazepine. Other ASDs such as phenobarbital, topiramate, and levetiracetam may be associated with mood and behavior lability. Therefore, these medications should be used with caution as a first-line treatment for epilepsy in depressed patients. In 2008, the US Food and Drug Administration (FDA) released a safety alert regarding an increased risk of suicidal behavior for patients treated with ASDs. Additional scrutiny has suggested that all ASDs carry an equivalent risk for depression, and the current consensus is that the risk associated with untreated epilepsy is far greater than the risk of AED-associated suicidal behavior.
4. Antidepressants, in general, are not contraindicated in patients with epilepsy, and treatment of comorbid depression in people with epilepsy is critical. Other than bupropion (which should be avoided as it increases the risk of seizures), commonly used antidepressants do not appear to lower the seizure threshold. Fluoxetine and paroxetine are strong inhibitors of hepatic enzymes and, therefore, may increase the levels of ASDs with co-administration, potentially leading to AED toxicity. This is easily avoided by monitoring serum drug levels and making adjustments as needed.
5. It is important to educate patients about the importance of treating *both* their epilepsy and their depression. Because many patients search the Internet for information about their diagnoses and medications, they are likely to have concerns about potential interactions and drug side effects. They should be reassured that the risk of stopping treatment—for either depression or epilepsy—far outweighs theoretical risks that may be associated with the use of their medications. Patients and their families should be counseled to watch for signs of depression and report any changes in mood or the presence of suicidal ideations. These signs should be taken seriously given the nature and chronicity of epilepsy.

If atypical deterioration of mood does occur as a result of the use of a particular AED, then practitioners should strongly consider changing that AED to an alternative agent.

Clinical Pearls

1. Depression, suicidality, and other psychiatric comorbidities are more common in people with epilepsy than in the general population.
2. Epilepsy and depression can—and should—be treated concomitantly. Physicians should consider an AED that has positive mood effects, such as lamotrigine, as a first-line agent for patients with depression. Avoid bupropion, but other antidepressants such as the selective serotonin reuptake inhibitors are not contraindicated in people with epilepsy.
3. Ask about mood and suicidal ideation at every clinic visit when treating people with epilepsy. Be ready to change your treatment plan if there are red flags that implicate AED-induced mood changes.

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Chapter 12
Brain Tumor and Epilepsy

Gregory D. Cascino and William O. Tatum IV

Case Presentation

A 30-year-old patient had a 3- to 4-year history of recurrent focal seizures. He was diagnosed with localization-related epilepsy manifested as recurrent focal seizures associated with a sudden behavioral arrest, vacant stare, and right upper extremity dystonic posturing. The duration was brief and was associated with postictal amnesia and word-finding difficulties. Rare nocturnal generalized tonic-clonic seizures also occurred. His neurological examination was unremarkable except for the mental status testing that demonstrated abnormal short-term memory. Routine EEG shows bitemporal epileptiform discharges which were most prevalent on the left during sleep. A CT of the brain was normal. The patient's seizures were refractory to phenytoin, carbamazepine, lamotrigine, and levetiracetam. MRI brain showed a focal lesion in the left medial temporal lobe (Fig. 12.1). The appearance suggested a primary brain tumor.

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W.O. Tatum et al. (eds.), *Epilepsy Case Studies: Pearls for Patient Care*,
DOI 10.1007/978-3-319-01366-4_12,

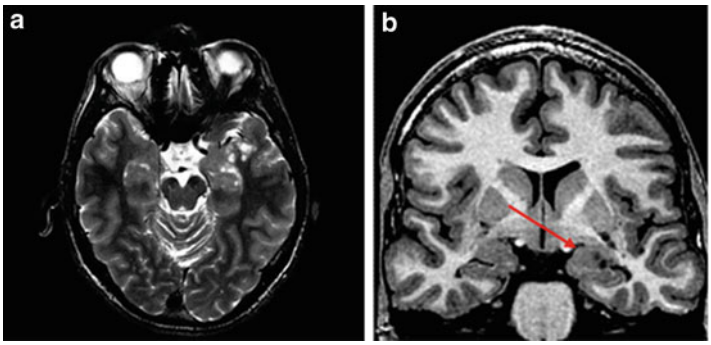

Fig. 12.1 Brain MRI with (**a**) axial T2-weighted and (**b**) coronal T1-weighted images of the *left* temporal lobe demonstrating a multi-cystic lesion (*arrow*)

Clinical Questions

1. What is the relationship of brain tumors to epilepsy?
2. What is the yield of brain MRI to demonstrate a lesion in epilepsy?
3. What are the common brain tumors that are associated with seizures?
4. What is the best recommendation for treatment?
5. What is the anticipated outcome of treatment and long-term clinical course?

Diagnostic Discussion

1. Many studies point to the frequent coexistence of brain tumors and epilepsy. Brain tumors are responsible for approximately 15 % of all adult-onset epilepsy. The more benign the tumor, the greater the risk of epilepsy. For example, low-grade gliomas have a high association with seizures (in some studies up to 80 %), while high-grade gliomas have a relatively lower association with seizures noted in approximately half of the number of patients who develop seizures. In addition, greater involvement to the cortex and to adjacent epileptogenic areas portends a greater likelihood that the tumor will be associated with seizures. Tumors are more common in the temporal lobe. Infratentorial tumors are uncommonly associated with seizure. The cell type of the tumor is also important. For example, a dysembryonal neuroepithelial tumor (DNET) is frequently associated with seizures more so than meningiomas or primary CNS lymphomas.
2. MRI head is the structural neuroimaging procedure of choice in patients with focal seizures and may demonstrate a lesion when a CT scan of the brain is normal. MRI brain is able to demonstrate pathological substrate and a medically

refractory partial seizure disorder. The imaging findings may strongly suggest a tumor type (i.e., meningioma or DNET) as in our patient, who was suggested to have a DNET or low-grade glial neoplasm based upon the imaging characteristics.

3. Tumors have been described with the highest frequency in temporal lobe epilepsy. Low-grade astrocytomas, gangliogliomas, meningiomas, DNET, glioblastoma multiforme, and lymphomas have been commonly associated with seizures. Seizures often herald the brain tumor and appear as the presenting symptom or early in the course of the disease. Most develop epilepsy, and up to 50 % of patients with tumor-associated epilepsy will become drug resistant to antiseizure drugs (ASDs). This is higher than other populations of patients with epilepsy. A role of genetic factors in tumor-associated epilepsy has been implicated in epileptogenesis.
4. Prophylaxis with ASDs should not be used in brain tumor patients who do not have seizures or epilepsy. No difference in intervention has been shown to be effective in preventing a first seizure using older ASDs. The grade of the tumor often drives the pursuit of surgical intervention. High-grade lesions and those that are believed to represent the potential for conversion to high-grade lesions should undergo complete lesionectomy if feasible for the best result. Even low-grade lesions may fair better with early resection and short epilepsy durations in the absence of drug-resistance. Drug-resistant localization-related epilepsy cases related to the tumor make excellent surgical candidates. Approximately 80 % of patients may be rendered seizure free subsequent to excision of the primary brain tumor and the epileptogenic cortex. Patients initially remain on ASDs, though selected individuals are candidates for AED taper and withdrawal.
5. Resection of the pathological lesion is the most effective procedure to render the patient seizure free. More tumors reside in the temporal region than extratemporal location. EEG monitoring confirmed the presence of left temporal lobe seizures in our patient. However, seizures may appear bizarre when the lesion lies in the extratemporal location (i.e., frontal lobe). Oftentimes in these cases, video-EEG may show unclear ictal onset and appear more subtle than MRI. Furthermore, video-EEG in up to 1/3 of patients may have the epileptogenic zone at a site removed from the tumor (dual pathology). Video-EEG should therefore be performed to characterize the relationship of the seizures to the lesion. Favorable predictors of seizure outcome are a short duration of epilepsy and complete resection of the tumor. Recurrent seizures after surgery should prompt a search for tumor regrowth. This patient underwent a left anterior temporal lobectomy. The pathology showed mild cortical gliosis and DNET. The patient was seizure free following surgery. Two years following surgery, the patient was successfully tapered off AED medication. Postoperative MRI did not reveal any definite tumor recurrence.

Clinical Pearls

1. MRI is superior to CT head scans for detecting brain tumor.
2. AED prophylaxis to prevent seizures and epilepsy is not indicated for patients with brain tumors.
3. Patients with focal seizures caused by foreign-tissue lesions (e.g., brain tumors) are much more likely to have drug-resistant seizures.
4. Brain tumors constitute an important cause of drug-resistant localization-related epilepsy. Temporal lobe tumors are most common and represent a surgically remediable epilepsy syndrome.
5. Video-EEG should be performed prior to lesionectomy to establish the relationship between the site of seizure onset and the MRI-identified lesion when seizure freedom is the goal.

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Chapter 13
Head Trauma and Posttraumatic Seizures

Jerry J. Shih

Case Presentation

A 44-year-old, right-handed, white male presents for an evaluation and opinion regarding the underlying etiology of his seizures. The patient had his first seizure in the summer of 2009. This occurred out of sleep. He noted significant work-related stress and alcohol usage the night before. His girlfriend awoke in the early morning hours when the patient experienced a generalized tonic-clonic seizure. He bit the left side of his tongue and had post-event confusion. He returned to sleep but had a second generalized tonic–clonic seizure 30 min later. EEG was normal awake and asleep. He was prescribed levetiracetam but did not take on a long term basis. He did well until October 2010, when he had a third nocturnal generalized tonic–clonic seizure. This event was preceded by sleep deprivation for over 24 h, significant alcohol use, and the use of cocaine. His girlfriend awoke to vocalizations associated with a convulsion. He was re-started on levetiracetam 500 mg twice daily. Review of risk factors for epilepsy disclosed that he had been involved in a motor vehicle accident in 1985 where he sustained a skull fracture that was associated with a loss of consciousness for approximately 5 days. He did not require neurosurgical intervention and recovered. He was later involved in an altercation in 1996 and was stabbed near his right eye, from which he also recovered. No family history of seizures, meningitis or encephalitis, stroke, brain tumor, brain surgery, migraines, collagen vascular disease, or febrile convulsions was evident. A brain MRI was obtained (Fig. 13.1).

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W.O. Tatum et al. (eds.), *Epilepsy Case Studies: Pearls for Patient Care*,
DOI 10.1007/978-3-319-01366-4_13, © Springer Science+Business Media New York 2014

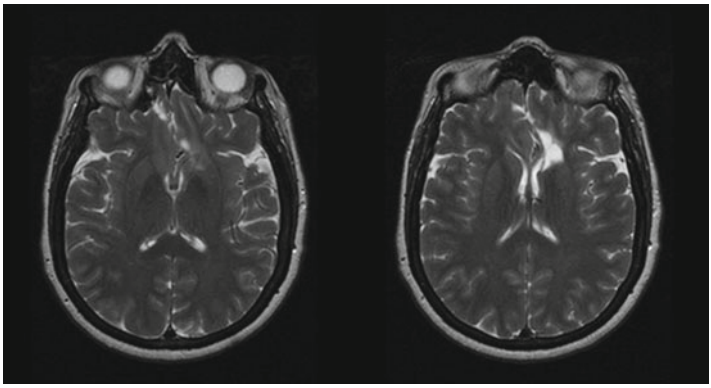

Fig. 13.1 T2-weighted brain MRI with bilateral frontal lobe encephalomalacia

Clinical Questions

1. How does the MRI help answer the patient's question?
2. What is his diagnosis?
3. What factors may affect his seizure control?
4. What is the best course of treatment?
5. What is the prognosis for developing epilepsy after a traumatic brain injury?

Diagnostic Discussion

1. The axial T2-weighted images show cystic encephalomalacia within the right orbitofrontal and left medial frontal region. Surrounding gliosis and ex-vacuo dilatation of the left frontal horn are also present. This is oriented along a linear trajectory extending from the medial right orbital roof. In this patient's case, the location likely represents the sequelae of a prior transorbital penetrating injury.
2. The patient has a clinical diagnosis of localization-related epilepsy, anticipated to be of frontal lobe origin. This diagnosis is supported by the MRI findings and by the generalized semiology of the seizures. The patient does not note an aura, though this is probably because his seizures arise out of sleep and are unable to be recalled. Frontal lobe seizures often occur during sleep, while temporal lobe seizures tend to occur while the patient is awake.
3. Posttraumatic epilepsy is the leading cause of new-onset seizures in young adulthood with acquired epilepsy. A number of factors may lower the seizure threshold in patients with epilepsy. Stress, sleep deprivation, intercurrent infections, medication noncompliance, and hypoglycemia have all been described as potential exacerbating factors. Drugs of abuse such as cocaine and amphetamines may also lower the seizure threshold.

4. The best course of treatment is based upon proper classification. His advanced age of onset and the abnormal brain MRI would be unlikely for someone with genetic generalized epilepsy. Aggressive management with antiseizure drugs directed at treatment for focal seizures should be undertaken. Accenting nighttime dosing and extended-release preparations (i.e., levetiracetam, lamotrigine, carbamazepine) may be useful choices. Given the MRI-defined structural abnormality that is often predictive of the epileptogenic zone, an epilepsy surgery evaluation is indicated if the patient continues to have debilitating seizures despite appropriate treatment with at least two first-line ASDs. Trauma acts as a negative predictor in patients that undergo temporal lobe resection.
5. The risk of epilepsy after traumatic brain injury (TBI) is influenced by the severity of head trauma. Military injuries are likely to carry a higher risk than civilian head injuries with only a small number of patients that develop posttraumatic epilepsy following mild, closed head injury. The risk of epilepsy is highest within the first year after the injury, but head injury remains a causal link to epilepsy for over 10 years. Seizures occurring "early" after a TBI within the first week are distinguished from "late" posttraumatic epilepsy because they differ in respect to mortality and prognosis of persistent seizures. Many early seizures do not recur as late posttraumatic epilepsy. Posttraumatic epilepsy is defined as seizures occurring at least 1 week after the acute injury. Although phenytoin may decrease early seizures within the first week after head trauma, no AED has demonstrated efficacy in stopping the development of posttraumatic epilepsy. Seizure recurrence may be higher than in those without a history of traumatic injury following control.

Pearls of Wisdom

1. The pattern of TBI that is present on brain MRI may help to explain the cause in patients with posttraumatic epilepsy.
2. "Early" seizures occurring within 24 h after injury do not predict the development of "late" seizures that occur beyond the first week post trauma in patients with posttraumatic epilepsy.
3. The risk of developing posttraumatic epilepsy remains high for many years after the acute injury. Additionally an underlying injury or an abnormal brain MRI carries a high risk for a second seizure.
4. Treatment with ASDs that render a patient with posttraumatic epilepsy seizure free have a greater risk of relapse following discontinuation. Trauma acts as a negative predictor when epilepsy surgery is considered.

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Chapter 14
Autonomic Seizures and Panayiotopoulos Syndrome

William O. Tatum IV

Case Presentation

A 9-year-old boy was evaluated for seizures. He has had a normal birth, labor, delivery, and development and was well until last year when he experienced a spell. He was playing outside when his mother went to check on him down by a pond. She noted that he suddenly developed a facial expression and "acted like he was going to be sick." He became pale, nauseated, wretched, and complained of being weak. His mom tried to encourage him to come inside and rest. The patient's father arrived and picked the patient up as he collapsed limply and then vomited. The patient was laid down on the ground when his eyes rolled up to the left; he became unresponsive, turned his head to the left, and briefly stiffened. Afterwards he was sleepy with urinary incontinence but fully recovered after a 3-h nap. In the ED, a CT brain was normal as were routine laboratory studies and a 12-lead EKG. Subsequently, a brain MRI revealed a left choroid fissure cyst. EEG demonstrated generalized spike-and-slow-waves (GSWs). He was diagnosed with absences, and ethosuximide was prescribed but declined by the parents. A computer-assisted ambulatory EEG captured a non-epileptic stare. Isolated GSWs were again noted throughout the recording (Fig. 14.1).

Clinical Questions

1. Does this EEG suggest a particular clinical diagnosis?
2. What is the clinical significance of the seizure?

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W.O. Tatum et al. (eds.), *Epilepsy Case Studies: Pearls for Patient Care*,
DOI 10.1007/978-3-319-01366-4_14,

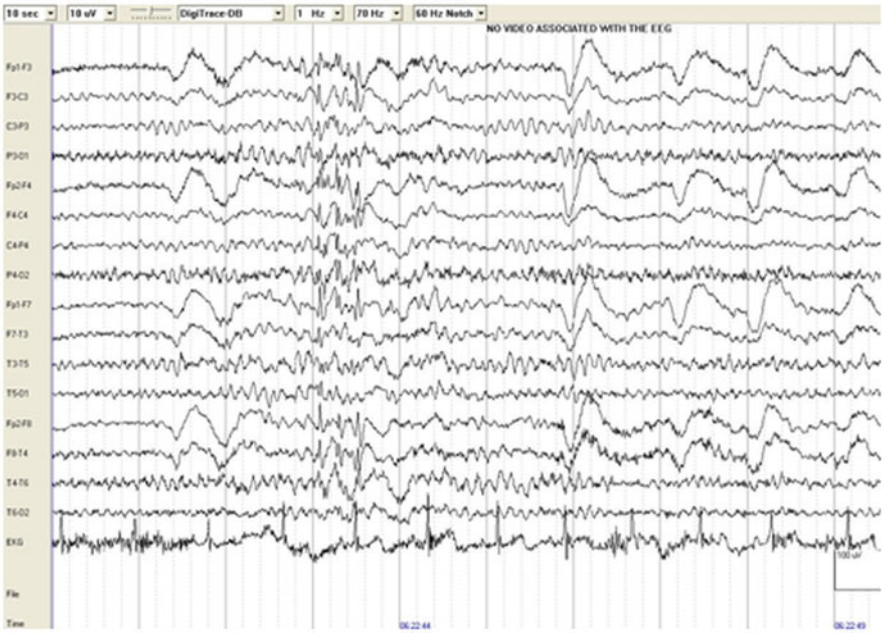

Fig. 14.1 EEG shows a brief burst of generalized spike-and-waves

3. What epilepsy syndrome is suggested?
4. What treatment should be recommended at this point?
5. What is the anticipated prognosis?

Diagnostic Discussion

1. An EEG that demonstrates 3-Hz GSWs suggests absence seizures. Absence seizures can vary in the clinical manifestations. This pattern however is not specific and may be seen with other epilepsies. Childhood absence epilepsy typically presents with multiple daily episodes of brief impaired responsiveness (absences). Myoclonus may occur during absence seizures but when prominent suggests epilepsy with myoclonic absences. If prominent eyelid myoclonia with absences is present with photosensitivity, Jeavons syndrome is suggested. In the teen years, other generalized seizures (i.e., myoclonus and convulsions) may occur with absence in juvenile absence epilepsy and juvenile myoclonic epilepsy. The genetic generalized epilepsies are suggested by GSW on EEG. However, it is the clinical phenomenology that defines the epilepsy syndrome. Furthermore, seizure types can overlap, even evolving from one epilepsy syndrome to another with time.

2. The patient's clinical event is characteristic of a prolonged autonomic seizure. Migraine and cyclical vomiting syndrome may be diagnosed initially, although, with a loss of consciousness and clonic jerking, the association with seizures becomes clarified. An autonomic seizure is an epileptic seizure characterized by altered autonomic function. Seizures may be focal or generalized at the onset with subjective or objective semiology composed predominantly of dysautonomia during the seizure. Nausea, vomiting, and other signs of autonomic dysfunction including changes in pupillary dilation, pallor or flushing, hypersalivation, temperature changes, and incontinence occur. Syncopal episodes may occur and are suggested by a limp, collapse, and pallor. In some children, autonomic seizures with syncopal-like episodes precede more characteristic seizure-like activity with hemiclonic jerking or convulsive motor movements. Autonomic seizures may be prolonged, lasting for half an hour or longer, reflecting autonomic status epilepticus. Typically autonomic seizures occur during sleep (similar to BCECTS; case 6), but in our patient occurred during wakefulness.
3. Panayiotopoulos syndrome (PS) is a recognized childhood epilepsy syndrome with an unusual seizure semiology which includes autonomic features in normal children. PS occurs in normal children and is manifested by infrequent autonomic seizures and autonomic status epilepticus. The onset is in childhood, usually before 6 years of age. Autonomic seizures typically present with symptoms of nausea and vomiting. Autonomic features may be the only symptoms present without the clonic jerking that is more readily associated with epileptic seizures. The nonconvulsive semiology may result in a delay in a diagnosis of epilepsy. Furthermore EEG may be normal, leading to misdiagnoses. Gastroenteritis, migraine, cyclical vomiting syndrome, encephalitis, and cardiac syncope may be suggested if the paroxysmal features are not witnessed. EEG abnormalities demonstrate marked variability with locations that include frontal, centrotemporal, multifocal, GSWs, and combinations of focal and generalized epileptiform discharges. When seen, occipital spikes predominate, are typically of high voltage, and can change significantly with repeat EEG recordings. Seizure may show shifting onsets with scalp EEG recording despite similar clinical manifestations.
4. Maintenance antiseizure drugs (ASDs) are often not required in PS due to the limited likelihood of recurrence. Most children have fewer than five seizures, though about 5 % of cases are recurrent. Many children may have only one or two seizures. Treatment may be considered if seizures are prolonged, associated with injury, psychosocially disturbing, or recurrent. While no single AED appears to show superiority, ethosuximide has activity against absence seizures, though it would not be expected to be beneficial for focal seizures. Video-EEG monitoring was discussed in the case of further events or if other seizure types (e.g., "phantom absences") became suggested clinically. Rescue medication with rectal diazepam gel was prescribed in the advent of autonomic status epilepticus. However, chronic maintenance ASDs were not prescribed. Lamotrigine was discussed as an option with recurrence due to the broad spectrum of activity in focal and generalized seizures without cognitive adverse effects.

5. The prognosis for PS is excellent and most remit in several years, though an earlier age of onset may be a negative predictor. The MRI brain was reviewed, and a small choroid fissure cyst identified, which was asymptomatic and incidental. Children with PS typically demonstrate normal development. PS, like other benign focal epilepsies of childhood, are probably linked due to a common, genetically determined, transitory functional derangement of the brain during the maturational process. A benign childhood seizure susceptibility syndrome has been used to describe a mild and temporary condition that enters remission as the child develops into adolescence and adulthood. The neuropsychological examination is normal except for visual and visuoperceptual alterations and infrequently minor attention and memory disturbances.

Clinical Pearls

1. Autonomic seizures and autonomic status epilepticus are not uncommon in childhood and may lead to misdiagnosis.
2. Panayiotopoulos syndrome is a unique childhood epilepsy syndrome with heterogeneous EEG features that carries a favorable prognosis.
3. Many patients with PS do not need treatment with chronic ASDs, though rescue medication in the advent of recurrent status epilepticus should be considered.
4. The prognosis for PS is excellent despite the prolonged seizures and syncopal-like episodes that may cause concern for underlying autonomic instability. When ASDs are required, most patients respond to treatment with spontaneous resolution.

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Chapter 15
Starting Antiepileptic Drugs

Kristen Marie Kathryn Kelly and Gregory D. Cascino

Case Presentation

A 44-year-old male experienced a single, unprovoked, generalized tonic–clonic seizure at 5:30 a.m. The seizure duration was approximately 2 min with gradual recovery following a postictal state. There was no prior history of seizures or predisposing neurological conditions or comorbidity. The only risk factor for epilepsy included a concussion as a child while playing sports. Additionally, the patient did have a sibling with childhood absence epilepsy. The patient was not on prescription medication at the time of the seizure. There was no history of alcohol abuse or illicit drug use. At the time, he was employed, operated a motor vehicle, and was married with two children. Upon evaluation in the emergency department, a CT of the head was normal. An EEG performed several hours after the seizure showed bitemporal independent sharp waves (Fig. 15.1). Other than complaining of a mild headache, myalgias, and a "sore tongue" the patient appeared to be doing well at the time of dismissal from the emergency department. An MRI head was subsequently performed and was unremarkable.

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DOI 10.1007/978-3-319-01366-4_15,

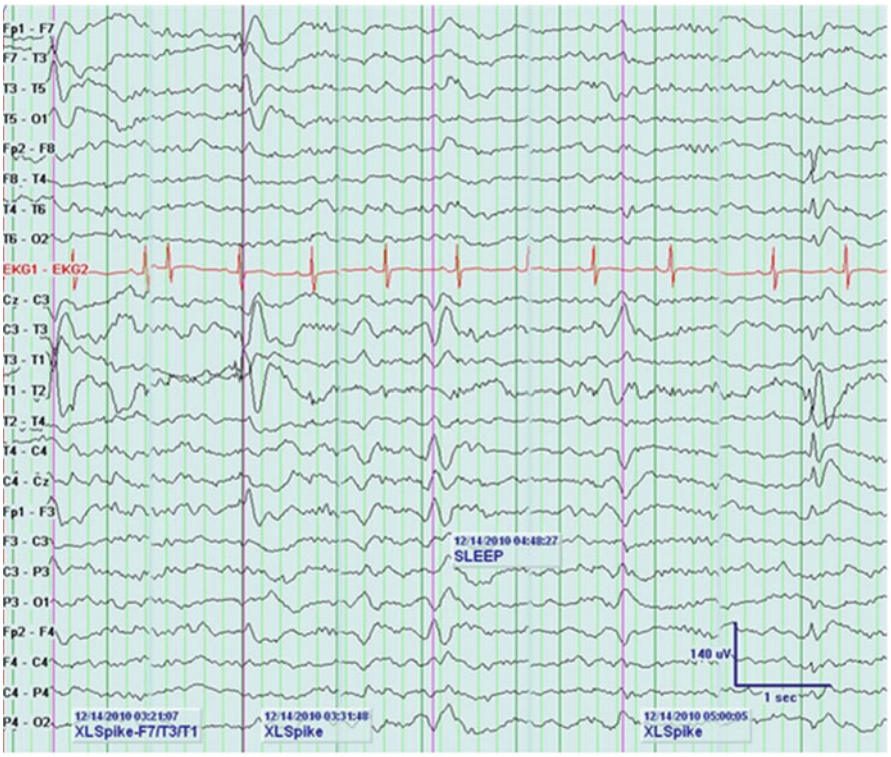

Fig. 15.1 EEG demonstrating independent bitemporal epileptiform discharges. Parameters of recording include sensitivity of 7 μV/mm; display speed 30 mm/s; and filter settings of 1–70 Hz

Clinical Questions

1. What is the likelihood of seizure recurrence?
2. What clinical risk factors increase the chance of recurrence?
3. What is the anticipated clinical course?
4. What should the patient do about driving?
5. What is the best course of treatment?

Diagnostic Discussion

1. Clinical studies have shown that the risk of seizure recurrence is 30–50 % at 2 years after a single unprovoked seizure. The likelihood of a second seizure is greatest in the initial 3 months following the seizure. The risk of a third seizure is approximately 65 % after a second seizure.

2. Clinical factors that *may* increase the risk of recurrent seizures include a preexisting neurological disorder, a focal neurological deficit, a history of remote symptomatic neurological disease, and a positive family history for epilepsy. An abnormal EEG recording with an epileptiform discharge and a lesion on neuroimaging are risk factors that carry a high likelihood of seizure recurrence.
3. The use of antiepileptic drug (AED) therapy to reduce seizure recurrence after a single unprovoked seizure needs to be individualized. AED medication has been shown in clinical studies to reduce the risk of seizure recurrence during short-term follow-up. However, there is no evidence that the use of AED therapy after a single seizure improves long-term seizure control in patients who develop a seizure disorder. The potential benefit of AED therapy needs to be contrasted with the potential adverse effects of medication. Important issues in patients who consider AED medication are the duration of therapy and the need for drug level monitoring. Patient compliance with medical therapy should also be considered in making a treatment decision (see response 5).
4. The laws regarding driving and epilepsy are determined by each state. Many of the restrictions are limited to patients with seizure disorders or epilepsy. The "seizure-free" duration period may range from 3 months to 1 year. Most states require self-reporting by patients. Medical forms may need to be completed prior to the individual being permitted to operate a motor vehicle. The patient should discuss the issue with the health care provider and review the individual state laws.
5. The clinical course is variable in patients who present with a single unprovoked seizure. Conditions where treatment may be warranted include a prolonged focal seizure or status epilepticus, the presence of an immediate family history, a neurological deficit, an abnormal MRI or EEG, and a remote seizure. From an individual patient perspective, those with high-risk jobs or an individual inability to accept a second seizure may warrant considering treatment. The occurrence of a second seizure would usually warrant AED therapy and careful monitoring of the patient. Approximately 80 % of patients with a seizure disorder have a favorable outcome with AED medication and nearly two-thirds of patients are rendered seizure free (see response 3).

Clinical Pearls

1. Single unprovoked seizures are very common and may not always indicate the onset of a seizure disorder (epilepsy). Most individuals will have recurrent seizures during the first year following the unprovoked seizure, with the highest risk being in the initial 3 months.
2. The use of AED therapy remains controversial for patients with a single unprovoked seizure. Selected patients may be considered for AED therapy. The evidence does not permit determination for the length or the dosing of AED therapy. Patients with a single unprovoked seizure should not be "over-treated" and may not need to have a "therapeutic" drug level to remain seizure free. A thoughtful

discussion with the patient about treatment should be performed prior to making a decision regarding the institution of AED medication.

3. As a general rule, the longer the patient remains seizure free after a single unprovoked seizure, the less likely there will be seizure recurrence. However, these individuals probably have a higher seizure tendency and should modulate behavior to try and avoid proconvulsant activities. Potentially, prolonged sleep deprivation, excess alcohol use, and illicit drug use may reduce the seizure threshold.
4. An abnormal EEG recording always needs to be interpreted in light of the clinical course for the patient. If the patient has a seizure, obtaining an EEG early the same day of the seizure may have a higher yield for demonstrating an abnormality. Epileptiform discharges when present support the clinical diagnosis of a seizure. In our patient, the bitemporal sharp waves support the diagnosis of a focal seizure.

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Chapter 16
Stopping Antiseizure Drugs

Kristen Marie Kathryn Kelly and Gregory D. Cascino

Case Presentation

A 32-year-old, right-handed white male with a history of well-controlled epilepsy is evaluated because he is interested in stopping his antiseizure drug (AED). He developed epilepsy manifested as infrequent focal seizures that evolved into convulsions when he was 28 years of age. He exhibited one type of seizure semiology and became seizure free following initiation of ASDs. The cause for his epilepsy was felt to be due to a motor vehicle accident which resulted in a traumatic brain injury. A brain MRI performed just after the accident showed a small amount of hemosiderin deposition in the right frontal lobe affecting the cortex. His current AED regimen is 1,000 mg of oral levetiracetam twice a day. He had not had a seizure in more than 2 years. He was working full time and was driving a car. While he does not report having any side effects from his medication, he does not like taking it, and is concerned about the cost of continuing use. His last EEG was performed 2 years ago and showed intermittent theta-delta slowing over the right frontal head region, but was otherwise normal (Fig. 16.1). His neurological examination in the clinic was normal.

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W.O. Tatum et al. (eds.), *Epilepsy Case Studies: Pearls for Patient Care*,
DOI 10.1007/978-3-319-01366-4_16, © Springer Science+Business Media New York 2014

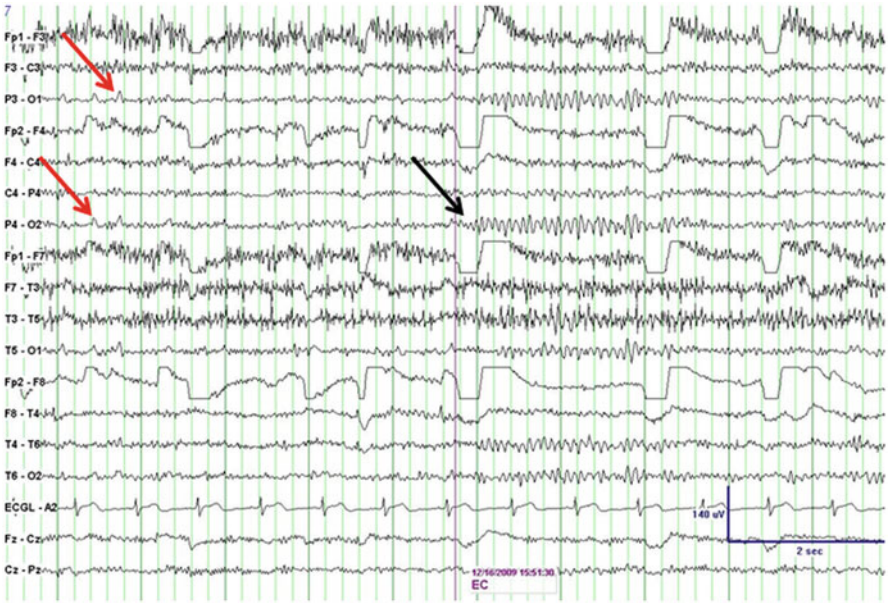

Fig. 16.1 EEG demonstrating a normal recording in the awake state with a well-formed 10 Hz alpha rhythm reactive with eye closure (*black arrow*). Note the normal lambda waves (*red arrows*)

Clinical Questions

1. What are the positive prognostic factors for seizure freedom upon discontinuation of ASDs?
2. What are the negative prognostic factors for seizure freedom upon discontinuation of ASDs?
3. Is it appropriate to consider discontinuing the AED for this patient?
4. What ancillary procedures may be of help in stratifying his risk of seizure recurrence?
5. How quickly should ASDs be tapered?

Diagnostic Discussion

1. Treatment with ASDs after an initial seizure reduces the risk of seizure recurrence by approximately 50 %. After a patient has remained seizure free for >2 years, favorable prognostic factors for seizure freedom after medication discontinuation include normal neurological exam and IQ, an EEG that normalizes after the initiation of ASDs, special epilepsy syndromes (e.g., childhood absence

epilepsy where remission likelihood is high), epilepsy that is readily controlled with AED monotherapy, a short duration of epilepsy, a single seizure type, and successfully undergoing lesionectomy for epilepsy.
2. Negative prognostic factors for seizure freedom after medication discontinuation include the presence of an abnormal neurological examination, epileptiform abnormalities on the EEG, special epilepsy syndromes (e.g., juvenile myoclonic epilepsy), the need for two or more ASDs prior to control, a long duration of uncontrolled epilepsy (i.e., more than 20 seizures), and the presence of a focal lesion on brain MRI.
3. After a patient achieves 2–5 years of seizure freedom on an antiepileptic medication (AED), most neurologists will discuss *a trial* of discontinuing ASDs. In women anticipating pregnancy, this should be first addressed after 2 years. In those that have syndromes that are long-lasting (e.g., JME) ASDs are typically for lifelong. This patient has positive prognostic factors for successful discontinuation of ASDs because his seizures are controlled with monotherapy; he has a single seizure type; he has a relatively short duration of epilepsy; and he has a normal neurological exam. A relatively negative prognostic factor is the presence of an abnormal MRI that may suggest seizure control as opposed to seizure remission where ASDs may be successfully tapered.
4. Further testing should include a repeat EEG. EEG has prognostic value in patients considering a trial of AED taper. In most studies, the presence of epileptiform suggests a higher likelihood of relapse when medication is withdrawn.
5. When the decision to taper ASDs is made, most patients do well. A slow taper schedule has been found to be more successful than regimens that stop medication abruptly. When breakthrough seizures do occur, half of the time it happens within the time period of drug taper and otherwise will occur within the first 3–6 months after patients are no longer taking ASDs. During this time it is best to continue seizure precautions, including temporarily restricting driving privileges.

Clinical Pearls

1. The average risk of seizure recurrence in patients with 2 years of seizure freedom upon discontinuation of ASDs is 20–50 %, depending on the individual's risk factors. If seizures do recur, many will occur in the first 6 months, and most will occur within the first 2 years after medication discontinuation.
2. Experts recommend withdrawing the AED slowly, tapering the medication over several months.
3. During a trial of AED taper, safety issues, especially driving, need to be discussed when counseling the patient. Temporarily restricting driving privileges should be recommended.
4. There are both positive and negative prognostic factors that can help determine an individual patient's likelihood of seizure recurrence. The presence of a lesion

on brain MRI and epileptiform discharges on EEG should have a relatively higher risk for relapse following a trial of AED taper.

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Chapter 17
Classification of Epilepsy

William O. Tatum IV

Case Presentation

A 20-year-old, right-handed, white female had drug-resistant epilepsy. She had failed several ASDs as single agents due to tolerability issues and had been maintained on Phenytoin for years. She was born via an uncomplicated delivery and was without any known risk factors for epilepsy. Seizure onset began at 9 years of age, manifesting as "petit mal" seizures. These occurred weekly and were worse after menarche. She was initially given Ethosuximide after an EEG demonstrated "petit mal seizure discharges," though she had incomplete improvement in her episodic staring spells. Subsequently, "grand mal" seizures developed within the year following puberty, and she was changed to valproate. She continued with intermittent "petit mal" seizures on a weekly basis. Trials of ASDs included VPA, Dilantin, and Ethosuximide were ineffective. TPM and LEV lead to side-effects of "memory problems" and severe anxiety. When she was seen for another opinion regarding pregnancy and driving, she was taking PHT 400 mg PO qHS which had provided her the best control thus far. Her neurological examination was normal. A CT of the brain was normal. A high resolution brain MRI with an epilepsy protocol was performed (Fig. 17.1). A computer-assisted ambulatory EEG demonstrated a staring spells associated with 2 Hz generalized spike-and-waves with normal background electrocerebral activity.

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W.O. Tatum et al. (eds.), *Epilepsy Case Studies: Pearls for Patient Care*,
DOI 10.1007/978-3-319-01366-4_17,

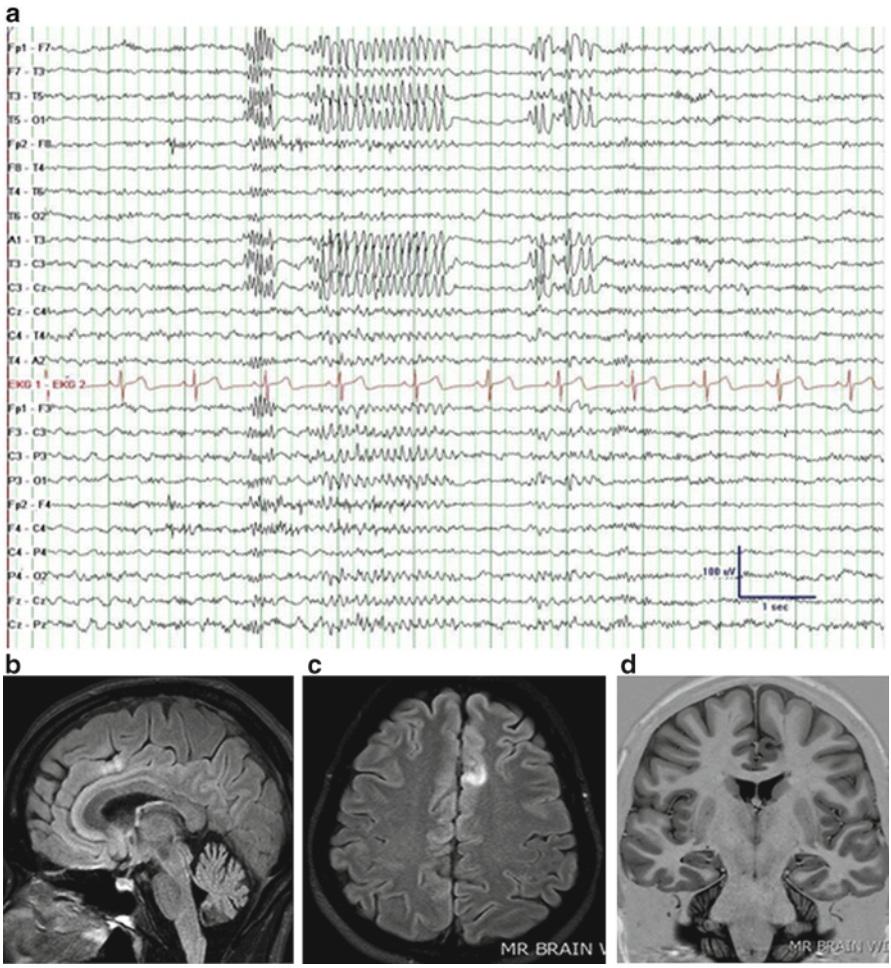

Fig. 17.1 (**a**) Interictal EEG demonstrating bilateral left hemispheric temporally predominant polyspikes. Note the temporal predominance despite the mesial frontal location of a lesion identified on brain MRI (**b–d**) with sagittal and transverse FLAIR, and coronal T1 images of a left mesial frontal lesion suggestive of cortical dysplasia. Note the cerebellar atrophy on brain MRI. EEG: longitudinal bipolar montage, sensitivity 7 μV, and filters 1–70 Hz

Clinical Questions

1. Does this patient have "petit mal" seizures?
2. How do the ancillary tests help classify the staring spells in this patient?
3. What type (classification) of epilepsy does this patient have?

4. What antiseizure drugs are appropriate for the corresponding classes of epilepsy?
5. What is the best course of action?

Diagnostic Discussion

1. This patient does not have true "petit mal" (aka absence seizures). Episodes of staring may be differentiated by a sudden stare for 10–15 s in absence while focal seizures with impaired consciousness typically last 30–40 s and manifest a warning (aura). Absence seizures begin and end abruptly while focal seizures often exhibit post-ictal disorientation and lethargy. Automatisms may occur in absence seizures that are longer in duration. Our patient is manifesting focal seizures, as supported by a focal lesion on brain MRI. Many patients refer to staring episodes as "petit mal" because they are mean to indicate to the non-convulsive nature of the events.
2. The EEG has left hemispheric predominant polyspikes. Generalized epileptiform discharges may occur in patients such as ours due to secondary bilateral synchrony. This bilateral diffuse epileptiform discharge occurs as a consequence of a localized process such as the left mesial frontal lesion. A generalized EEG pattern is probably due to the proximity of the lesion to the corpus callosum. Mesial frontal lesions have a rapid transit time via the callosum to manifest as bilateral synchronous epileptiform discharges on the EEG. There may be a "lead in" to generalized discharges that can appear, and the generalized spikes (or polyspikes) usually have a repetition rate of <3 Hz when it occurs. In this case, the burst of polyspikes is lateralized to the left and the brain MRI clearly shows an area of FLAIR abnormality that probably reflects focal cortical dysplasia to strengthen the classification of the seizures in this case.
3. This patient has localization-related epilepsy manifest as brief focal seizures with impaired consciousness and focal seizures that evolve to convulsions. Focal seizures that evolve to convulsions are a commonly recognized entity in patients with localization-related epilepsy. In addition, lateralized semiologies and EEG features may occur in patients with generalized seizures associated with genetic epilepsy (i.e., JME) are common. Terminology and concepts for reorganization of the epilepsies have been recently performed dichotomizing common focal and generalized seizures. Overlap between generalized and focal seizures may rarely occur. The clinical onset of absence ("petit mal") with subsequent convulsions "grand mal" suggests one of the genetic generalized epilepsies. However secondary bilateral synchrony on the EEG (and generalized discharges from a focal lesion) or focal abnormality on brain MRI suggests focal seizures as the correct classification.
4. Treatment is predicated upon proper seizure and epilepsy classification. Narrow-spectrum ASDs such as carbamazepine and phenytoin may aggravate seizure control or worsen some generalized seizure types (absence and myoclonic

seizures). Similarly, some ASDs for generalized seizures (ethosuximide) as in this case may be ineffective for the treatment of focal seizures. EEG is fundamental to seizure classification when semiology is unclear, such as when dealing with staring episodes and convulsions. Even EEG may be challenging when a lack of defining interictal discharges or secondary bilateral synchronous epileptiform discharges are present. Brain MRI may reveal a focal lesion (as in this case) that supports localization-related epilepsy and guide AED choices for focal seizures. Most ASDs have been approved by the US Food and Drug Administration for clinical use in the treatment of focal seizures. Valproate, lamotrigine, topiramate, levetiracetam, and zonisamide have demonstrated efficacy in some patients with both focal and generalized seizures. The barbiturates and benzodiazepines may also demonstrate benefit in both seizure types.

5. The best course of action for this patient is to treat her for drug-resistant seizures. Following the failure of two appropriate AsDs for an adequate time period, the substitution or addition of alternative agents carries a low yield of success. Because our patient has a definable lesion on brain MRI, surgical therapy was recommended, which she refused, noting that her seizures were not a "disability" for her. A change to Lamotrigine as a non-enzyme inducing AED was also recommended given the long-term consequences that were possible on PHT with uncontrolled seizures; however, she felt too comfortable with her treatment to accept a change. Her wishes were respected, and she continues to have infrequent seizures. She has since delivered two healthy children on PHT monotherapy.

Clinical Pearls

1. Petit mal is a common colloquialism used by patients to reflect non-convulsive staring spells. Adults reporting "petit mal" and "grand mal" seizures beginning after adolescence likely reflect focal epilepsy with focal seizures with/without impaired consciousness and focal seizures that evolve to convulsions.
2. Brain MRI may be a useful ancillary test in the classification of epilepsy in patients with poorly defined stereotyped events. Furthermore, it may support localization (in this case, the frontal lobe). EEG is the most useful test when the brain MRI is normal or nonspecific. When clear focal or generalized interictal epileptiform discharges are present, this supports the diagnosis of epilepsy and the mechanisms for the recurrent seizures. However, secondary bilateral synchrony may occur in patients with extratemporal epilepsy, as in this case, which may make it more difficult to distinguish from a primary generalized discharge.
3. Broad-spectrum, antiseizure drugs are useful treatments when the classification of the seizures and epilepsy type is unknown. These agents are effective for both focal and generalized seizures and do not aggravate a specific seizure type.
4. Drug-resistance is a definable entity and a prerequisite to epilepsy surgery independent of a need for surgery based upon a lesion. However the acceptance of

epilepsy surgery by patients is an individual decision and one that is relative to their seizure type and self-perceived disability.

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Chapter 18
Epilepsy in Older Adults

Joseph I. Sirven

Case Presentation

A 75-year-old female is seen in the emergency department (ED) due to a subacute onset of severe back pain. The pain is centered in the mid-thoracic area of the back without radiation and is easily exacerbated by movement. She is an established patient and has a history of localization-related epilepsy with recurrent focal seizures. The seizures were caused by a previous stroke that occurred almost a decade ago. The typical seizure manifests as a generalized convulsion. In the past, they had been sporadic and had occurred in both the day and nighttime. The patient also reports persistent imbalance and a feeling of chronic dizziness. She has been adherent to her current dosage of phenytoin taken as directed by her neurologist. She is taking 300 mg per day with a recent serum level of 10 mg/dl. The patient had been on a higher dose of phenytoin in the past but complained that she experienced significant problems with her balance. In the ED, following clinical assessment, a radiograph of the thoracic spine was performed. The interpretation suggested a compression deformity in the appropriate area. An MRI is performed and reveals the following (Fig. 18.1):

Clinical Questions

1. What does the radiograph show?
2. How should dosing and titration of antiseizure drugs be performed in older individuals?
3. Should certain antiseizure drugs be avoided?

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W.O. Tatum et al. (eds.), *Epilepsy Case Studies: Pearls for Patient Care*,
DOI 10.1007/978-3-319-01366-4_18,

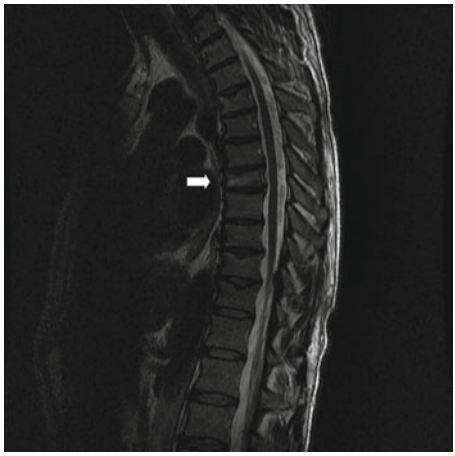

Fig. 18.1 MRI of the thoracic spine demonstrating a compression fracture at T8 with evidence of edema reflecting the subacute onset (*arrow*)

4. What does a serum level of 10 mg/dl of phenytoin in this patient suggest about their therapeutic level?
5. What are the implications for bone health in older patients on certain antiseizure drugs?

Diagnostic Discussion

1. The X-ray demonstrates a compression fracture of the thoracic spine (see arrow in figure). This is likely a result of a pathologic compression fracture as the result of a seizure, given the thoracolumbar location of the abnormality. Individuals with epilepsy, particularly older women, often have a particular predilection towards bone fractures due to osteopenia and osteoporosis. This needs to be considered when treating seizures in all ages, as enzyme-inducing antiseizure drugs (ASDs) such as phenytoin can markedly increase the risk of osteoporosis in patients with epilepsy.
2. When initiating any antiepileptic drug in an older patient with epilepsy, it is important to observe the adage of "go slow and low" when using ASDs. If the dose of ASDs, as well as other medications, is increased too quickly, neurological adverse effects such as ataxia, dizziness, gastrointestinal upset, and cognitive issues will often make the drug intolerable due to side-effects, leading to poor patient adherence or facilitating other medical comorbidities such as falls, weight loss, and memory impairment.
3. Although there are no absolute contraindications to using any of the ASDs in older adults, there are some general caveats. Phenytoin is particularly problematic for the older adult patients and should probably be avoided. This AED often

causes imbalance, increases the risk for osteoporosis, and may lead to cardiac conduction problems. Moreover, there are limitations with respect to regulating serum drug concentrations, a number of drug–drug interactions that are associated with its use. This can make the management of the older adult with epilepsy taking phenytoin quite complex and difficult. Newer ASDs without these difficulties now exist, which permit far better options in selecting an AED.

4. Most laboratory serum levels drawn to assess concentrations of antiseizure drugs are based on younger age groups. The fact that this older patient had a serum level of 10 μg/dl does not imply that it will be effective or devoid of side-effects. Due to slower metabolic function and delayed renal clearance, serum levels in older adults must be judged in the context of the clinical setting. For example, a patient with a serum phenytoin level of 10 μg/dl may report significant adverse effects and appear "toxic." A low total serum concentration may be due to low protein binding or due to drug–drug interactions involving ASDs and non-ASDs. Judging the clinical impact of the AED chosen is most important as opposed to simply adhering to a numerical level.
5. Phenytoin as well as other enzyme-inducing antiseizure drugs can increase the risk factors of osteoporosis in both younger and older adults. Agents such as phenytoin, phenobarbital, primidone, carbamazepine, among other weaker enzyme-inducing antiepileptic agents (i.e., topiramate and oxcarbazepine) may lead to a greater risk of osteopenia and osteoporosis. The mechanism is either through interacting with vitamin D absorption or metabolism preventing calcium absorption or utilization or by other mechanisms that are yet to be identified. Understanding these relationships is important in selecting an AED in older adults with favorable pharmacokinetics such as levetiracetam or lamotrigine that may be effective but that is less likely to produce similar complications.

Clinical Pearls

1. Seizure incidence becomes more likely with age due to other associated neurologic conditions that are commonly encountered during the process of aging. Stroke is the most common cause of first seizures in people under 60 years of age, although other symptomatic causes including dementia also become notable comorbidities.
2. It is essential that one use lower doses and slower titration to avoid adverse effects. Adverse effects are the most common cause of problems in the older adults, as these individuals tend to be on multiple medications.
3. Choosing medications with the fewest drug–drug interactions and daily or twice daily dosing are good choices for an older adult, given the prevalence of polypharmaceutical uses in addition to issues of impaired cognition and the risk of cumulative adverse effects.
4. Enzyme-inducing antiseizure drugs should be avoided in older adults, given the risk of osteoporosis, gait instability, and the risk of pathological fractures.

5. Serum levels in older adults must be judged within the context of the patient's clinical presentation. A "normal" serum AED level does not confirm the absence of clinical toxicity.

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Chapter 19
Progressive Myoclonic Epilepsy

William O. Tatum IV

Case Presentation

A 19-year-old, right-handed female of mixed Caucasian and Mediterranean decent presented to an epilepsy clinic with a diagnosis of "seizure disorder." At 14 years of age she experienced her first generalized tonic–clonic seizure. Subsequently, she developed multifocal myoclonus and was diagnosed with the Juvenile Myoclonic Epilepsy (JME) syndrome. However, she gradually worsened with uncontrolled frequent daily generalized myoclonus and monthly convulsions that were resistant to multiple antiseizure drugs. Over the years, her grades fell, and dedicated neuropsychological testing demonstrated a slow reduction in full scale IQ into the 60s. She developed difficulty walking with frequent falls and ultimately became wheel-chair dependent. Seizures became refractory to multiple broad-spectrum ASDs. Neurological examination revealed a young female awake and cooperative but with psychomotor slowing, visual inattention, and dysarthria. She relied on single-word answers and hand gestures. Gait revealed an unsteady ataxic gait. Her brain MRI was unrevealing, and an EEG was abnormal (Fig. 19.1).

Clinical Questions

1. Does this patient have JME?
2. Does this EEG support a particular clinical diagnosis?
3. What are myoclonic epilepsy syndromes to be considered and what are the defining characteristics for them?

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W.O. Tatum et al. (eds.), *Epilepsy Case Studies: Pearls for Patient Care*,
DOI 10.1007/978-3-319-01366-4_19,

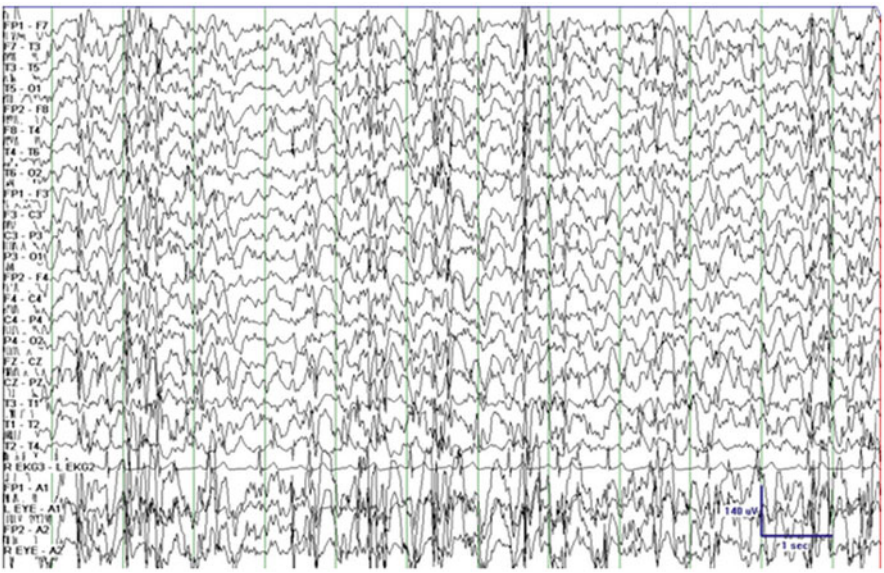

Fig. 19.1 EEG showing diffuse slowing of the background activity punctuated by nearly continuous generalized spike and polyspike discharges. Note the occipital predominant sharp waves. EEG parameters include a bipolar montage, sensitivity of 7 μV/mm, and filters of 1–70

4. What diagnostic testing should be considered?
5. What is the anticipated clinical course and prognosis with the expected diagnosis?

Diagnostic Discussion

1. JME is a common genetic generalized epilepsy that manifests in adolescence. It is characterized by repetitive irregular myoclonic jerks predominately involving the upper body. No loss of consciousness is encountered unless the patient manifests generalized (clonic)–tonic–clonic seizures. Nearly all JME patients have GTC seizures with myoclonic seizures (one-third also have absence seizures). Seizures occur with morning predominance and require long-term therapy. Interictal EEG demonstrates 3–5 Hz generalized spike- and polyspike-and-waves and photosensitivity is common. In our patient, the clinical presentation of myoclonic and convulsive seizures early on may suggest JME, but the progressive course and the abnormal EEG background activity suggests otherwise. The progressive course with worsening of mental status, gait, dysarthria, and uncontrolled seizures suggests one of the progressive myoclonus epilepsies (PME).
2. The EEG findings of the frequently intermixed generalized spike- and polyspike-and-waves would suggest generalized epilepsy. However, the diffusely

slow background activity would suggest an encephalopathic process as opposed to JME. PME has EEG changes that may precede the clinical symptoms by 6 years. Diffuse slowing and generalized IEDs occur in virtually everyone. Slowing and loss of an alpha rhythm gradually became replaced by generalized IEDs with occipital predominance in addition to focal and multifocal abnormalities. The IEDs wane during sleep unlike genetic generalized epilepsy where the IEDs become more prominent. Giant somatosensory evoked potentials and increased cortical excitation to paired pulse transcranial magnetic stimulation may be seen. The myoclonus of PME is a prominent clinical feature though, in addition, generalized, focal, and atypical absence seizures may also occur.

3. The progressive myoclonus epilepsies (PME) are a rare group of disorders (Table 19.1). Unverricht–Lundborg disease, Lafora disease, myoclonic epilepsy with ragged red fibers (MERRF), the adult form of neuronal ceroid lipofuscinosis (Kufs), and sialidosis are the principal PMEs. Our patient presented in early adolescence and at first mimicked JME. The progressive cognitive decline, worsening myoclonus, dysarthria, and gait disorder led to a clinical diagnosis of Lafora Disease (LD). LD presents in early adolescence and may initially mimic IGE though progressively worsening myoclonus after an initial GTC signals a different course. Slow cognitive decline, visual impairment, visual hallucinations, and occipital seizures become evident. Progressive myoclonus, refractory epilepsy, dementia, ataxia, and speech dysfunction occurs. Total care is evident prior to a fatal demise which occurs within 10 years after onset.
4. MRI brain may identify atrophy in the more aggressive PMEs. Basal ganglia signal changes may be seen in MERRF but were absent in our patient. In our patient, EEG demonstrated a diffusely slow background with frequent GSW and PSW coupled with myoclonic jerks. SSEPs were performed without high amplitudes of the N19 waveform to median nerve stimulation. Genetic testing is helpful to establish the diagnosis. In our patient, EPM1 and EPM2 were normal. A point mutation on tRNALys gene was not recovered. An axillary skin biopsy was without Lafora bodies but did demonstrated intracytoplasmic “fingerprint” inclusions and lipofuscin pigment stored in the lysosomes characteristic of adult NCL (Kuf’s disease).
5. The prognosis for patients with PME is oftentimes poor. Treatment is usually supportive. ASDs chosen should have broad spectrum utility due to the possibility of narrow spectrum ASDs aggravating seizures. Valproate is useful, though needs to be avoided in MERRF. Lamotrigine may worsen myoclonus in some. Neurostimulation may have a role for some. Unverricht–Lundborg disease has the most favorable prognosis. The epilepsy is usually less refractory to ASDs though phenytoin is contraindicated. Patients may become wheelchair bound, though the cognitive decline may be mild and the course tends to stabilize over time. Our patient with Kuf’s requires complete care and has already become wheelchair bound. Her rapid deterioration reflects a poor prognosis. Most patients with PME, including adult NCL and Lafora disease, have limited lifespans with the course culminating in death within a decade. Genetic markers are helpful, though biopsy may still be required for confirmation.

Table 19.1 Comparison of the progressive myoclonus epilepsies

	Onset (years)	Clinical features	EEG	Pathology	Outcome
Unverricht–Lundborg	6–18	Myoclonus, GTC seizures, ataxia, dysarthria, tremor. Become wheelchair dependent. Mental decline late	Similar to GGE at onset with worsening background activity over time with GSW and PSW	Recessive mutation in cystatin B a protease inhibitor (EPM1) on chromosome 21	Long-term survival
Lafora	6–19	Rapidly progressive myoclonus, epilepsy, blindness, and mental decline. Occipital seizures, absence, GTC	Normal at the beginning, declining over time. Background slowing with GSW, PSW and occipital IEDs	Autosomal recessive polyglucosan stored in sweat glands on biopsy. EPM2A and EPM2B on chromosome 6	Death usually within 10 years of onset, often from status
MERRF-MELAS	Childhood to adolescence	Abrupt or slow onset of generalized myoclonus, epilepsy, and ataxia. ± Spasticity, deafness, ocular defects. Lactic acid and stroke-like episodes in MELAS	EEG background activity slows with progression. GSW and focal IEDs. Photosensitive and photomyoclonic	Point mutations of tRNALys gene (most maternal inheritance). Atrophy and signal changes evident in basal ganglia on MRI brain antemortem	Variable course
Adult NCL	Adolescence early adulthood	Dementia ataxia and later myoclonus and seizures. Normal vision in contrast to other forms of NCL	Background activity is slow with GSW. Photosensitivity at 1–3 Hz. Enlarged SSEPs	Autosomal recessive lipopigment storage in the lysosomes. Fingerprint inclusion on axillary skin biopsy	Death usually within 10 years
Sialidoses	Adolescence early adulthood	Action and intention tremor and GTC seizures. Cognitive decline. No real visual deficit	Few IEDs and low amplitude fast background activity. Myoclonus with 10–20 Hz central activity. Large SSEPs and reduced VEPs	Autosomal recessive deficiency of neuraminidase A. Sialidated oligosaccharides in urine. Vacuolated Kupffer cells on histology	Variable course

GTC generalized tonic–clonic, *GGE* genetic generalized epilepsy, *SSEPs* somatosensory evoked potentials, *IEDs* interictal epileptiform discharges, *VEPs* visual evoked potentials

Clinical Pearls

1. PME is a rare epilepsy syndrome caused by a heterogeneous group of disorders. PME may mimic JME at the onset of the clinical course due to the presence of myoclonus and convulsions but is soon defined after the onset by progressive neurological deterioration.
2. Diffuse slowing of the background with GSW and PSW occurs with time and suggests one of the encephalopathic generalized epilepsies with myoclonus. Neurophysiological studies may additionally demonstrate enlarged evoked potentials in some reflecting the cortical hyperexcitability that are encountered in PME.
3. The PMEs are a rare group of patients with progressive neurological deterioration with seizures comprising <1 % of the epilepsies. Unverricht–Lundborg disease, Lafora disease, MERRF, NCL, and sialidosis are the primary types of PME seen that are represented by this group of conditions.
4. Genetic testing and enzyme identification is usually helpful in establishing the diagnosis in the appropriate clinical context of PME. By identifying the precise molecular defect in individual disease states, an etiological diagnosis is possible. Axillary skin biopsy may be useful in confirming Lafora bodies and inclusions seen in adult NCL. Muscle biopsy may be confirmatory in MERRF.
5. The prognosis is usually unfavorable with disability and wheelchair-bound states when survival occurs. Seizures often become resistant to ASDs. Some courses are slower than others though usually neurological deterioration to a premature death is the rule. No disease modifying treatments are available at this time and treatment is with broad spectrum ASDs and is otherwise supportive.

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Chapter 20
Metabolism and Antiseizure Drugs

William O. Tatum IV

Case Presentation

A 57-year-old black male had hypertension, diabetes, end-stage renal failure, and was on hemodialysis (HD) three times weekly for 4 h. He was seen in the Emergency Department (ED) locally after presenting with a generalized seizure 3 h after arriving home from HD. His past medical history had included two similar generalized seizures. A first seizure occurred during HD. It was convulsive but was not treated because it was felt to reflect fluid and electrolyte shifts. The second one was considered an unprovoked seizure, though the patient declined treatment after an EEG was normal. He later insisted that it was provoked by his "medical condition." On examination in the ED, he was lethargic but aroused to tactile stimulation. He was disoriented to date and person and confused about the situation. A relative weakness was present in his left arm and leg, and a posterior-lateral tongue laceration was present. He was given 1,000 mg of Levetiracetam (LEV) intravenously. Laboratory studies revealed a creatinine of 10.1 mmol/ml and blood urea nitrogen was 36 mmol/ml. Hemoglobin was 11.1 g/dl with hypochromic microcytic indices. MRI revealed subcortical white matter microvascular ischemic change. An electroencephalogram (EEG) and neurology evaluation were ordered, and he was admitted for further evaluation (Fig. 20.1).

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W.O. Tatum et al. (eds.), *Epilepsy Case Studies: Pearls for Patient Care*,
DOI 10.1007/978-3-319-01366-4_20,

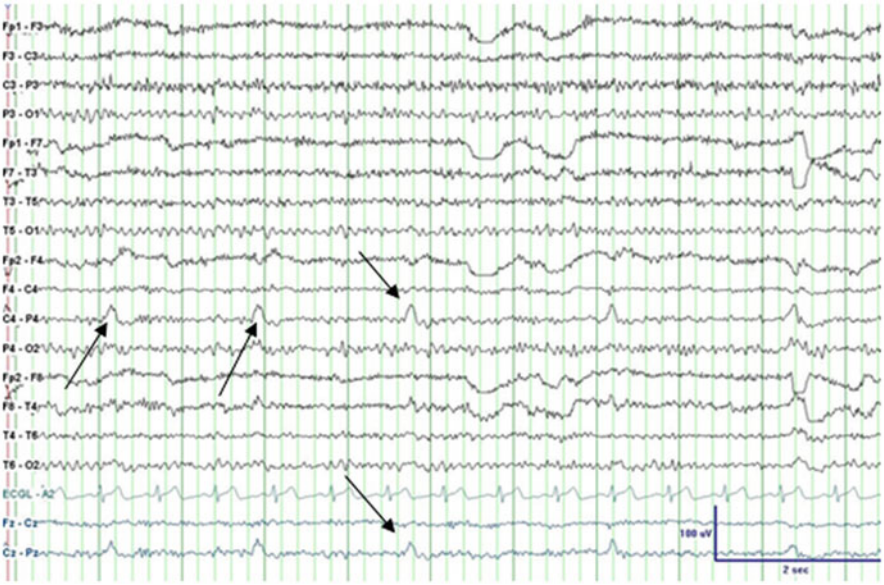

Fig. 20.1 EEG shows right regional frontocentral periodic lateralized discharges (*arrows*) on the anterior-posterior bipolar montage. Display speed 30 mm/s; filters 1–70 Hz; sensitivity 7 μV/mm

Clinical Questions

1. Does this EEG suggest a specific clinical problem?
2. How is the EEG helpful in supporting a clinical diagnosis and treatment?
3. How common are seizures in renal failure?
4. How is AED dosing altered in systemic illnesses?
5. What is the best course of treatment?

Diagnostic Discussion

1. The EEG obtained demonstrates right frontocentral Periodic Lateralized Discharges (PLDs). PLDs consist of repetitive epileptiform discharges usually recurring in periodic intervals every 0.2–3 Hz. Variable amplitudes and fields are present with most PLDs declining over weeks. PLDs are usually an epiphenomenon of an underlying structural lesion though the etiology is nonspecific. Most PLDs occur after acute large structural destructive lesions involving the cortex. Stroke is the most common clinical cause of PLDs though anoxia, tumor, infection (e.g., Herpes simplex encephalitis) may also be causative. PLDs may also occur as a post-ictal state, as in our patient, and may rapidly defervesce.

Approximately half of patients with PLDs that do not have seizures beforehand develop epilepsy with survival of the acute illness.

2. Most PLDs are usually not considered an ictal manifestation on EEG. However they may be ictal especially when they repeat, are very frequent, and when appropriate clinical symptoms align. Clinical seizures occur in approximately 80 % of patients with PLDs. Electrographic seizures without clinical manifestations may occur with even greater frequency. Mental status alteration, focal neurological deficits, and focal motor seizures, including epilepsia partialis continua are often present. PLDs are a feature of EEG that lie within the interictal–ictal continuum. While a 20 min routine scalp EEG recording may demonstrate PLDs and suggest an interictal feature on EEG, continuous EEG may reveal clear electrographic seizures at later times during prolonged recording and provide evidence for ongoing seizures and even status epilepticus. In our patient, the PLDs resolves as he recovered clinically without further seizures. The abnormal EEG demonstrating focal epileptiform abnormalities supported the diagnosis of focal seizures and the need for chronic antiseizure drugs.
3. About 10–30 % of patients with renal insufficiency develop seizures. Most are associated with hemodynamic shifts and associated fluid and electrolyte changes. In the case of provoked seizures during HD from an electrolyte imbalance, or from an untoward effect of medication (e.g., bupropion), ASDs are not required. Symptoms of cerebral edema including headache, visual changes, confusion, and nausea surrounding HD sessions reflect the rapid clearance of urea and may predispose to seizures. Focal and generalized seizures may develop in acute renal failure from uremic encephalopathy. Chronic renal failure may be associated with abnormal EEG patterns that rarely include focal epileptiform discharges except during HD. Renal transplantation may quickly reverse any EEG abnormalities in renal failure within weeks. Post-transplant use of immunosuppressive agents, however, may be proconvulsant and increase the likelihood that patients with a propensity to epileptic seizures require chronic ASDs.
4. Altered metabolic states are becoming frequent due to the greater number of patients living with renal and hepatic insufficiency. While chronic illnesses such as hypertension and diabetes occur frequently and lead to compromised renal and hepatic function, patients with epilepsy may also become compromised in their metabolic function due to the effects of ASDs. The degree and need for alterations in AED therapy for patients with renal and hepatic failure is drug-specific (Table 20.1). For dose adjustments the pharmacokinetics of the AED including the route of elimination must be known. HD alters the response to ASDs and may make supplementation necessary. Protein binding alteration in liver and kidney disease may necessitate changes in dosing. Frequency in dosing may change due to a reduction in the elimination half-life. Nomograms are available for most ASDs in the package insert to assist the clinician with dose changes.
5. Renal transplantation is the best course of treatment for chronic renal failure. Both renal and hepatic failure increases the risks of infection, neoplasm, and seizures. Our patient was activated for renal transplantation and was continued on LEV. The major route of excretion is renal; however, the broad spectrum

Table 20.1 Antiseizure drugs with renal and hepatic dosing recommendations

Drug	Renal dosing	Hepatic dosing
Carbamazepine	Low albumin may increase free levels. No dosing adjustments needed	Rare hepatic reactions and accumulation of toxic metabolites
Clobazam	No dose adjustments in mild to moderate dysfunction. No experience in severe dysfunction or in HD	Start at 5 mg/day for mild to moderate dysfunction, titrate dose every 7 days to 10–20 mg/day in divided doses. No dosing recommendations for severe dysfunction
Ethosuximide	No dose adjustments recommended. 38–54 % removed in HD, no supplemental dose required	No dosing adjustments
Ezogabine	Initiate dose at 50 mg tid, with increases no more than 50 mg tid/week to max 200 mg tid	Initiate dose at 50 mg tid with increases no more than 50 mg tid/week to max 250 mg tid in mild to moderate dysfunction; and 200 mg tid in severe dysfunction
Felbamate	Use half of starting and maintenance dose	Contraindicated in liver disease or preexisting liver disease; associated with increased risk of hepatic failure
Gabapentin	CrCl 30–60 ml/min: bid dosing CrCl 15–30 ml/min: daily dosing CrCl <15 ml/min: every other day dosing 200–300 mg supplementation after each 4 h of HD	No dosing adjustments
Lacosamide	No dosing adjustments for mild to moderate dysfunction. Max daily dose of 300 mg in severe impairment (CrCl <30 ml/min) or in ESRD. Dosage supplementation of up to 50 % following 4 h of HD	Maximal recommended dose of 300 mg/day in mild to moderate dysfunction. Not recommended in severe dysfunction
Lamotrigine	17 % removed after 4 h of HD; use with caution in ESRD	Give half starting and maintenance dose in severe dysfunction
Levetiracetam	CrCl 30–50 ml/min: 250–750 mg bid CrCl <30 ml/min: 250–500 mg bid ESRD: 500–1,000 mg daily 250–500 mg supplemented after HD (not XR formulation)	No dosing adjustments for mild to moderate dysfunction. Give half dose if severe cirrhosis (Child-Pugh C)
Oxcarbazepine	Initiate at lower dose (daily vs. bid) and increase dose slowly	No dosing adjustments in mild to moderate dysfunction

(continued)

Table 20.1 (continued)

Drug	Renal dosing	Hepatic dosing
Perampanel	Clearance decreased by 27 % and AUC increased by 37 % in mild to moderate dysfunction. No adjustments in mild dysfunction (CrCl 50–80 ml/min); not studied in severe dysfunction or in HD	AUC increased 1.8-fold in mild dysfunction, 3.3-fold in moderate dysfunction; drug half-life prolonged to 306 and 295 h, respectively. Start at 2 mg/day and inc by 2 mg/day every 2 weeks to max 6 mg/day (mild) and 4 mg/day (moderate). Not studied in severe dysfunction
Phenobarbital	No dosage adjustments unless CrCl <10 ml/min, then decrease dose. May need dose changes in HD or PD	May need to decrease dose
Phenytoin	CrCl >25 ml/min: minimal protein binding changes, no dosage adjustment needed CrCl 10–20 ml/min: decreased protein binding, unpredictable CrCl <10 ml/min: affinity for albumin decreases twofold Higher doses may be needed in hemofiltration	Chronic liver disease will increase free levels due to decreased protein binding
Pregabalin	CrCl >60 ml/min: 600 mg/day, divided bid-tid CrCl 30–60 ml/min: 300 mg/day, divided bid-tid CrCl 15–30 ml/min: 150 mg/day, divided daily-bid CrCl <15 ml/min: 75 mg daily 25–75 mg supplemented with every 4 h of HD	No dosing adjustments
Rufinamide	No dosage adjustments for CrCl <30 ml/min. 30 % decreased exposure with HD, consider adjusting maintenance dose	Not recommended in severe dysfunction, although has not been studied. Use with caution in mild to moderate dysfunction
Tiagabine	No dosage adjustments needed	Decrease starting and maintenance dose and/or longer dosing interval may be needed
Topiramate	Give half normal dose; supplemental dose may be required in HD	Decreased drug clearance
Valproate	Low albumin may increase free levels	Contraindicated in liver disease or severe dysfunction. May see increased free levels

(continued)

Table 20.1 (continued)

Drug	Renal dosing	Hepatic dosing
Vigabatrin	AUC inc by 30 % in mild dysfunction; twofold increase in moderate, and 4.5-fold increase in severe dysfunction. Start at a lower dose CrCl 50–80 ml/min: decrease dose by 25 % CrCl 30–50 ml/min: decrease dose by 50 % CrCl 10–30 ml/min: decrease dose by 75 % 40–60 % removed by HD, not adequately studied	No dosing adjustments required, although not studied
Zonisamide	Not much information known; may require slow titration upwards	No dosing adjustments

Courtesy of Sarah L. Clark, Pharm.D., R.Ph.; Updated 13 December 2012
Sources: Micromedex®, Facts and Comparisons®, drug package inserts

efficacy, tolerability, lack of drug–drug interactions and intravenous form make it a good AED choice for patients on multiple medications. In renal failure, the half-life of LEV is prolonged and accumulation of this AED occur requiring maintenance dose reduction. Furthermore 50 % of the pool of the drug is removed during routine HD and may require supplementation to approximate baseline post-HD drug-levels. Our patient has been seizure-free on LEV 250 mg in the morning and 125 mg in the evening daily, supplemented with 250 mg dose post-HD with stable serum concentrations.

Clinical Pearls

1. PLDs are usually seen with a structural lesion, though may also be seen as a post-ictal phenomenon on EEG following a convulsive seizure, indicating a focal epileptic mechanism.
2. PLDs carry a strong association with clinical seizures. Unless clinical resolution is evident, continuous EEG may help with the diagnosis and treatment of ongoing electrographic seizures.
3. Renal and liver failure impair metabolism of ASDs and often require alteration in routine treatments to ensure efficacy without toxicity.
4. Drug-specific alterations are required for ensuring adequate treatment and are based upon pharmacokinetic profiles of individual ASDs represented in nomograms contained within the drug package inserts.

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Chapter 21
Driving and Epilepsy

Joseph I. Sirven

Case Presentation

A 41-year-old female pilot for a major airline presented with subacute worsening of brief events of involuntary stereotyped motor movements. The episodes began 3 years ago and until recently were sporadic. They consisted of an abrupt onset of left arm posturing with elevation toward her face and "smacking her lips." At the same time she reported that her left face would draw upward associated with a transient inability to verbally respond to questions. The episodes were several seconds in duration and occurred three times daily on average. She reported that they were so brief that they did not impact her cognition or impair her overall ability to function. Worsening began following a long airplane flight where she had been sleep-deprived due to a busy and difficult work schedule causing them to occur several times an hour. Her general and neurological examination was normal. An MRI was obtained and was found to be normal. A serum drug screen and laboratory was unrevealing. An EEG was subsequently obtained and captured an episode (Fig. 21.1).

Clinical Questions

1. How does the EEG assist in the diagnosis?
2. What implications does the diagnosis of epilepsy have for driving?
3. What implications does the diagnosis of epilepsy have for flying?

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W.O. Tatum et al. (eds.), *Epilepsy Case Studies: Pearls for Patient Care*,
DOI 10.1007/978-3-319-01366-4_21, © Springer Science+Business Media New York 2014

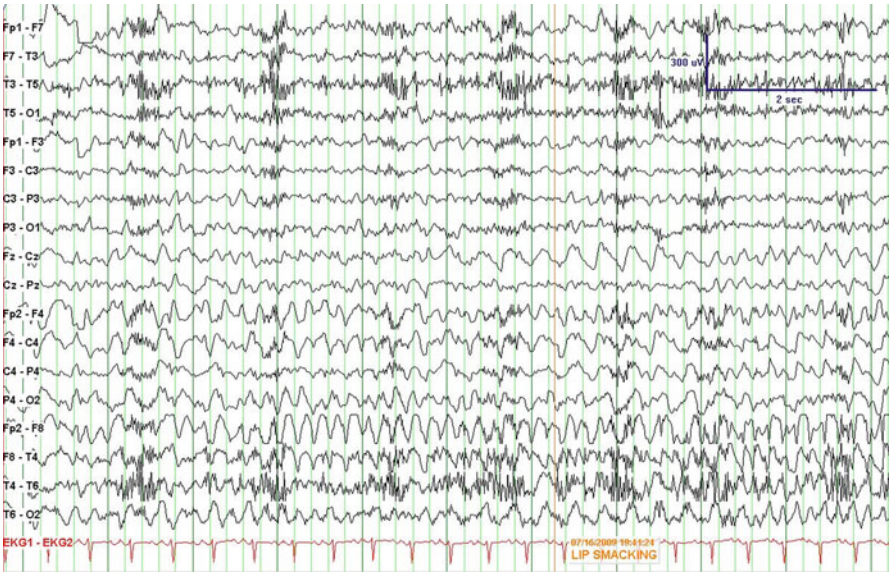

Fig. 21.1 EEG demonstrating a brief focal seizure with left arm extension during right frontal 10 Hz activity. Note the arousal from sleep following the event

4. What implications does the diagnosis of epilepsy have for the patient who is a commercial truck driver or railroad engineer?
5. What are your responsibilities in reporting this information?

Diagnostic Discussion

1. The EEG demonstrates an electrographic seizure manifest as generalized left frontally predominant burst of rhythmic 10 Hz alpha frequencies. This discharge was recorded during one of the individual's typical events and occurred directly from sleep. As such, given the clinical aspect of the diagnosis, this ictal EEG would confirm the diagnosis of localization-related epilepsy consisting primarily of focal seizures with left-sided motor symptomatology.
2. Individuals who experience an unexplained loss of consciousness, seizures, or epilepsy are subject to state driving laws. The state laws vary and depend upon the individual state of licensure. Most states require a seizure-free interval to maintain driving privileges. State laws vary from a minimum of 3 months to a maximum of 1 year in the USA before legally being able to operate a motor vehicle.
3. Given that the patient has a diagnosis of epilepsy, the issue of piloting any plane is governed by Codes and Regulations set forth by the Federal Aviation Administration as part of the Department of Transportation. As such, this indi-

vidual would need to show that they have been seizure free for nearly a decade without a diagnosis of epilepsy to independently operate an airplane. Commercial pilots are subject to even more rigorous restriction. Moreover, for this individual to return to flying airplanes, they need to be completely off of their seizure medications.

4. Commercial interstate trucking licenses as well as railroad engineers also fall under federal regulations by the Department of Transportation. This individual would also need to show that they have been seizure free for a prolonged time period (governed by individual state law) and well controlled by ASDs prior to release to truck driving. Chauffeur class A and B licenses are subject to even tighter control.
5. All 50 states mandate that physicians counsel their patients regarding their individual state driving laws. This should be documented in the patients' clinic chart. Six states including Delaware, New Jersey, Pennsylvania, California, Oregon, and Nevada have additional requirements that mandate physician reporting of all patients presenting with seizures to the state medical bureau. Failure to report individuals with epilepsy to the state bureaus could result in loss of physician licensure. The legal issue of the mandatory reporting of patients who have seizures to the department of motor vehicles or other federal bureaus is controversial. The American Academy of Neurology does not support the position of universal reporting. Under the current laws with the exception of reporting states, unsafe or risky drivers may electively be reported if they are deemed a safety risk without fear of impunity.

Clinical Pearls

1. It is essential that all patients be counseled with regard to transportation issues including driving, engineering, flying, and operating heavy machinery.
2. Physicians need to be aware that counseling patients is relative to regulations defined by individual state law as well as federal law.
3. The physician–patient relationship needs to be protected when delivering information regarding driving restriction. It is important to provide an explanation in a manner that is nonjudgmental so that patients understand that you are not writing the rules but rather adhering to legal policy. We do not need to function as the driving police. Rather the onus of personal responsibility falls on the patient to self-report. The physician's role is to act as a patient counselor and to serve as a patient advocate in appropriate circumstances.
4. Patients should also be counseled about any cognitive adverse effects related to ASDs that may impair their ability to operate a motor vehicle. Certain states do have driving under the influence laws and certain ASDs may be subject to scrutiny in some states (i.e., controlled substances). Familiarity with the state driving laws is an essential component to care for patients with seizures and epilepsy.

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Chapter 22
Frontal Lobe Epilepsy

Lily Wong-Kisiel

Case Presentation

A 24-year-old right-handed woman sought a second opinion regarding recurrent spells. They began at 6 months of age and occurred spontaneously without provocation. Her medical history showed she had been diagnosed with clinical depression and obstructive sleep apnea syndrome, supported by polysomnography. There were no risk factors for epileptic seizures. She had only one type of clinical event, which occurred during sleep and upon wakening. The events were approximately 30 s in duration and occurred daily, sometimes up to ten times per night. Brain MRI and routine EEGs were normal. Prolonged video-EEG recorded numerous stereotypic events characterized by arousal from sleep, rolling over into the prone position, right hand hyperflexion posturing, repeatedly sitting up, and then lying down with kicking and body rocking. During this time, the EEG was obscured by movement artifact. However, during some of the events, the EEG showed rhythmic 3–4 Hz activity that appeared to evolve in the midline frontal and central head regions (Fig. 22.1).

Clinical Questions

1. What is the differential diagnosis for childhood onset paroxysmal events?
2. What features differentiate psychogenic non-epileptic attacks from epileptic seizures?
3. What is the diagnostic gold standard in this case?
4. Why are the EEGs repeatedly normal?
5. What are the features of frontal lobe epilepsy?

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W.O. Tatum et al. (eds.), *Epilepsy Case Studies: Pearls for Patient Care*,
DOI 10.1007/978-3-319-01366-4_22, © Springer Science+Business Media New York 2014

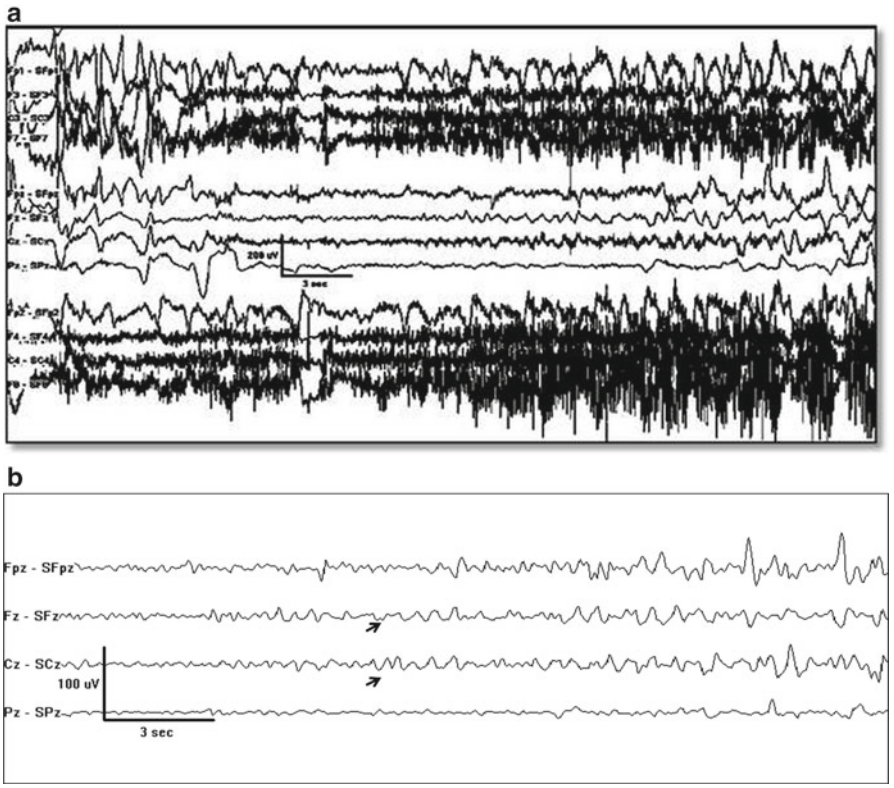

Fig. 22.1 (**a**) Scalp ictal EEG showed rhythmic 3–4 Hz activity evolving over the midline frontal and midline central head regions during an event, indicative of a seizure. (**b**) The "coned down" view with *arrows* demonstrating the evolution during the event

Diagnostic Discussion

1. Paroxysmal events can be epileptic or non-epileptic. Non-epileptic childhood onset paroxysmal events due to physiologic causes may include jitteriness, movement disorder, self-stimulation, syncope, transient metabolic disorders, gastroesophageal reflux (Sandifer syndrome), or sleep disorders. Terminology for paroxysmal non-epileptic events due to psychological causes, "pseudoseizures," has changed due to negative connotation. Psychogenic non-epileptic seizure (PNES) is now the preferred term, reflected in the current literature, to avoid the implication of being false that the prefix "pseudo" implies. Epileptic seizures may be mistaken as non-epileptic if the semiology includes psychiatric symptoms. Mesial temporal lobe seizures may be associated with psychiatric symptoms such as anxiety, panic attacks, déjà vu, jamais vu, and auditory or visual hallucination. Frontal lobe seizures may be brief and occur without postictal confusion. They may manifest as bizarre behaviors with prominent

vocalization and complex bimanual–bipedal motor automatisms. Epilepsy and psychiatric illness frequently coexist, which makes the diagnosis more challenging.

2. Clinical features of PNES vary and lack consistency in the episodic behavior within an individual patient. Prolonged events, a waxing and waning or "on-off" course, non-stereotypical writhing motor movements or flailing, thrashing, side-to-side head movements, asynchronous body movements, forward pelvic thrusting, and eye closure with resistance to passive eye opening are concerning symptoms for PNES. PNES do not arise from sleep and may be intensified by a bystander. Epileptic seizures are stereotypic. Eye closure can, on rare occasion, occur with epileptic seizures, but it is typically not seen during the entirety of the seizure. Tongue bites are located posterior-laterally in patients with epileptic seizures. Frontal lobe seizures can present with complex and bizarre motor movements, but these seizures are brief, 5–20 s, and tend to cluster in sleep. Prominent axial body movement can begin abruptly, and the patient may turn to the prone position during frontal lobe seizures. This is not typically seen in patients with PNES. PNES may occur with epileptic seizures though this only occurs in about 10–15 % of patients. Injuries can occur in both PNES and epileptic seizures, though serious injury should raise the suspicion of epilepsy. Reliance on clinical features may result in diagnostic error requiring video-EEG monitoring for a definitive diagnosis.
3. Video-EEG, with capture of the typical event, is the diagnostic gold standard to differentiate PNES from epileptic seizures. A typical event must be recorded during prolonged video-EEG to differentiate between epileptic seizures and PNES. Frontal lobe epilepsy can be challenging to diagnose, even with simultaneous EEG and video analysis because the EEG is often obscured by muscle artifact or, at the scalp, may appear normal. When juxtaposed frame by frame, frontal lobe seizures for an individual patient follow the same stereotyped sequence and motor repertoire.
4. Frontal lobe seizures and focal seizures without impaired consciousness may elude detection by scalp EEG with up to 30 % of patients not demonstrating interictal epileptiform discharges on repeat recordings. Many patients with FLE may have a generator that is cortically based in the frontal lobe where low-voltage fast frequencies are generated (and only seen at the cortical surface), or the generator is deep in the midline structures not amenable to routine scalp EEG recording. Antiepileptic drug discontinuation may be necessary to elicit more frequent and more intense seizures to reveal ictal EEG findings on scalp monitoring. Even a normal ictal EEG excludes the possibility of frontal lobe epilepsy.
5. Frontal lobe seizures are typically frequent, brief, occurring in clusters, predominantly nocturnal, and often occur without significant loss of awareness. Clinical characteristics depend on the brain regions generating the seizures. Seizures from the primary motor cortex present with contralateral clonic movements or dystonic posturing. Supplementary motor area involvement manifests as synchronous, asymmetric tonic seizures that may include the fencer's posture (forced head turn to the side of extended arm, contralateral to the side of seizure

onset, and ipsilateral arm elevation and elbow flexion). If awareness is impaired, recovery is quick, without prolonged postictal confusion. Seizures involving the mesial frontal lobe may exhibit bizarre automatism and pronounced hypermotor activity such as running around in circles, rocking back and forth, leg bicycling, jumping out of bed, and spitting. Vocalization, including yelling, swearing, and screaming, may occur in up to 30 % of patients. The bizarre and emotional semiology may suggest a psychiatric origin to the behavior (pseudoseizure), yet this seizure is epileptic (pseudo-pseudoepileptic seizure). Rotational body movement can occur so that the patient appears to turn in a circle. Orbitofrontal seizures can present as hypermotor seizures or appear similar to mesial temporal lobe seizures demonstrating oral and manual automatism with altered awareness. Frontal polar seizures may also present as hypermotor seizures.

Clinical Pearls

1. Paroxysmal events can be non-epileptic psychogenic, non-epileptic physiologic, or epileptic seizures. Relying solely on the clinical semiology may result in diagnostic error.
2. Epilepsy and psychiatric illness may coexist, making the diagnosis of epileptic seizures challenging.
3. Paroxysmal non-epileptic behavioral events lack consistency in contrast to epileptic seizures, which are stereotypic. However, patients with non-epileptic events may atypically also have concurrent epileptic seizures.
4. Video-EEG with recorded event is the diagnostic gold standard to differentiate non-epileptic from epileptic events. A normal interictal and even ictal EEG does exclude the possibility of epilepsy, especially when it involves the frontal lobe.
5. Frontal lobe seizures are characteristically brief, tend to cluster, occur during sleep, and manifest with hypermotor semiologies that appear bizarre. Classic semiologies of specific frontal lobe regions include symmetric or asymmetric tonic seizures and fencer's posturing seen in supplementary motor area seizures. Orbitofrontal seizures can mimic focal seizures that emanate from the mesial temporal region.

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Chapter 23
Pregnancy and Epilepsy

Amy Z. Crepeau and Gregory D. Cascino

Case Presentation

A 28-year-old right-handed female came to the clinic 3 days after her first seizure. The seizure occurred out of sleep and was described by her boyfriend as a convulsion. The emergency medical service took her to the nearest hospital where she was diagnosed with new-onset generalized tonic–clonic seizure. The patient was amnestic for the event and was without memory recall until she arrived at the hospital. She had no significant past medical history and did not use alcohol or illicit drugs. She worked in marketing and had been very successful in her career. Her routine and neurological examinations were unrevealing, excepting the post-ictal state. A CT of the head and routine laboratory assessment, including a urine drug screen, were normal. She recovered gradually to baseline and was discharged from the emergency department with neurological consultation planned. There were no definite triggers and she had no risk factors for epilepsy. She lived alone but had a steady boyfriend with whom she planned to marry and have children. She was seen for neurological evaluation and discussion of family planning. A brain MRI was performed and was normal. A routine outpatient EEG was performed and showed bursts of generalized anterior-predominant 3 Hz spike-and-slow-waves, consistent with Genetic Generalized Epilepsy (Fig. 23.1). The patient was subsequently started on lamotrigine (LTG) and told to refrain from operating a motor vehicle. During titration of LTG, she experienced a second generalized tonic–clonic seizure 2 weeks later,

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W.O. Tatum et al. (eds.), *Epilepsy Case Studies: Pearls for Patient Care*,
DOI 10.1007/978-3-319-01366-4_23, © Springer Science+Business Media New York 2014

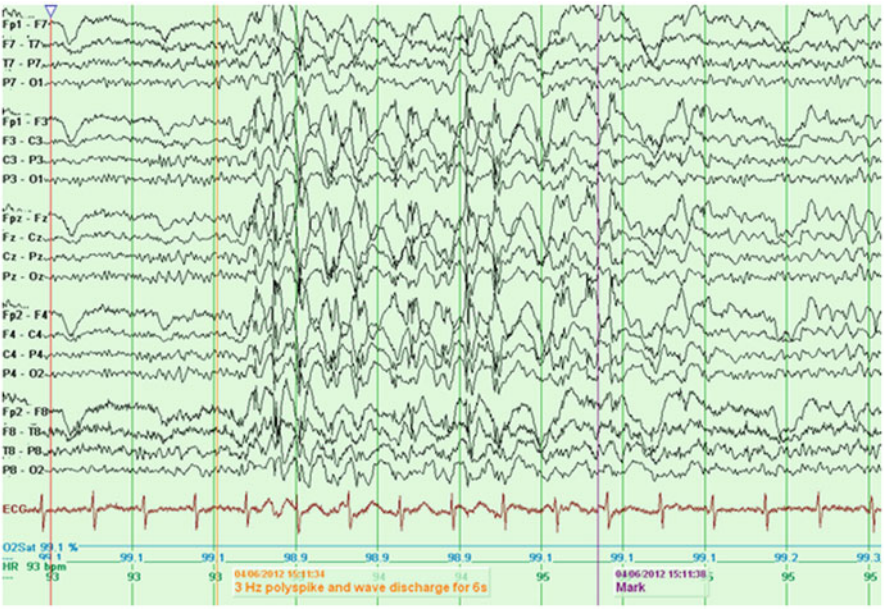

Fig. 23.1 EEG demonstrating a burst of generalized anterior-predominant 3 Hz spike-and-slow-waves

which occurred at work. Her employer was nervous about her returning to work, due to concerns that she would have a seizure at work, and that a diagnosis of epilepsy would impact her ability to perform her job.

Clinical Questions

1. If she does want to start a family, what risks are associated with being on ASDs during pregnancy?
2. Are there ASDs that would be preferred and ones that should be avoided?
3. Is there a risk to the baby if she has seizures during pregnancy?
4. What is the risk of worsening of seizure frequency during pregnancy?
5. Is she at higher risk for pregnancy complications?
6. What are the risks after delivery for women with epilepsy and their babies?

Diagnostic Discussion

1. Some women with epilepsy (WWE) find it harder to conceive. Gynecological problems including menstrual irregularities, polycystic ovaries, and catamenial seizures may complicate the course of treatment. In addition, WWE may have a greater risk of pregnancy-related problems including vaginal bleeding, risk of

Table 23.1 The approach to management of epilepsy and pregnancy

Preconception	Pregnancy	Postpartum
Optimize seizure control	Monthly serum AED levels	Serum AED levels
Folic acid supplementation	Seizures and side-effects	No evidence of harm due to AED exposure in breast feeding
Smoking cessation		
Monotherapy, if possible		Minimize sleep deprivation
Consider teratogenic risk of specific AED		
Baseline serum AED levels		

prematurity, small-for-gestational-age babies, and other obstetric risks. However, most can safely become pregnant while on ASDs. This does require planning by the patient and physician (Table 23.1). The goal in AED use during pregnancy is monotherapy with the lowest dose required for efficacy. The overall prevalence of major congenital malformations of children born to mothers with epilepsy is 4–10 %. This is two to four times higher than in the general population, and can vary depending on which drugs are used, the number of drugs used, and their doses. Polytherapy has consistently been associated with an increased risk of congenital malformations by comparison to monotherapy.

2. AED selection, in regard to potential for fetal malformations, should be made before the patient becomes pregnant. In general, LTG and levetiracetam appear to have the lowest risk of fetal malformations, though carbamazepine, and perhaps oxcarbazepine, may be relatively safe too. Valproic acid has consistently been associated with an increased risk of major congenital malformations, compared to other ASDs, in multiple large pregnancy registries worldwide. Phenobarbital has also been associated with a greater teratogenesis in those treated in the USA. Phenytoin has an intermediate risk. Valproic acid has also been associated with lower postnatal IQs in children up until 6 years of age when they are exposed in utero within the first trimester. The relative risks of using newer ASDs or requiring VPA when a dose <1,000 mg is compared to polytherapy are not yet established. Risk of major congenital malformations may be decreased by supplementation of at least 0.4 mg of folic acid daily.
3. Generalized tonic–clonic seizures during pregnancy can result in fetal harm due to traumatic injury, resulting in fetal bradycardia and systemic lactic acidosis. The impact of focal seizures, with or without impaired consciousness, and absence seizures on the developing fetus is not known. Still, focal seizures with impaired consciousness have been shown to alter placental blood flow and should be treated. In general, any seizure that could potentially result in harm to the mother is dangerous to the baby during pregnancy.
4. Change in seizure frequency during pregnancy is unpredictable, though seizure freedom in the 9 months prior to pregnancy has been found to be predictive of seizure freedom during pregnancy. Averaging all studies, approximately 50 % of WWE have no change in seizure frequency, 25 % have an increase in seizure frequency, and 25 % have a decrease in seizure frequency. However, these numbers vary with individual studies.

5. Most WWE have uneventful pregnancies. For WWE on ASDs, there is probably no substantially increased risk of bleeding late in pregnancy or Caesarean section, and likely no moderately increased risk of premature contractions, labor, or delivery. There is a higher risk of premature labor and delivery in WWE who smoke, and smoking cessation should be encouraged prior to conception.
6. After delivery, there may be risk of breakthrough seizure due to decreased serum AED levels and sleep deprivation. Children born to WWE carry a higher risk of developing epilepsy later in life, though the risk is related to the underlying etiology for epilepsy.

Clinical Pearls

1. Most WWE can safely become pregnant while on ASDs with a slightly increased risk of fetal malformations. Preconception planning and coordination between her neurologist and a high-risk obstetrician is required beforehand. Fluctuations in the volume of distribution, bioavailability, and metabolism during pregnancy require close monitoring of AED serum levels and likely changes in doses at different stages of pregnancy.
2. There is a differential effect of ASDs on the fetus. Valproic acid should be avoided if possible for the individual patient. Levetiracetam and lamotrigine appear to carry a relatively lower risk of congenital malformations. Using low doses and monotherapy optimize outcomes for WWE during pregnancy.
3. Potential harm from generalized tonic–clonic seizures during pregnancy outweighs the risk from ASDs. WWE have a higher risk of death during pregnancy, for reasons which are unclear. Overall there is a low risk, but continued seizure control during pregnancy is crucial in minimizing morbidity and mortality in both the mother and the baby.
4. Supplementation with folic acid should be maintained to minimize the risk of birth defects. Most WWE have normal healthy children.

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Chapter 24
Hormonal Replacement Therapy

Katherine Noe

Case Presentation

A 40-year-old woman developed seizures in early adolescence following viral encephalitis. She described her typical seizures as beginning with a feeling of fear and a peculiar sensation rising up from her epigastric region. This was followed by staring and unresponsiveness with repetitive lip smacking. She was diagnosed with localization-related epilepsy and was prescribed numerous ASDs that failed to work for her. She is currently on monotherapy lamotrigine and has a vagus nerve stimulator. She was previously evaluated for epilepsy surgery, but was found to be a limited candidate. The high-resolution MRI of her brain was normal and bilateral independent focal seizures arising from the left and right temporal regions were present on inpatient video-EEG monitoring. Seizures were occurring once every 4–8 weeks, but in the last 2 years they had increased to 1–3 times per month. Breakthrough seizures always clustered around her menstrual period. She was once treated with acetazolamide begun the week prior to her menses; however, this was discontinued as her periods had become increasingly irregular over the last 2 years. She is now having frequent hot flashes and night sweats that significantly disrupt her sleep. She brings in a diary in which she has charted her seizures and her menstrual periods. Examples of the months in which a menstrual period occurred with seizures are shown in Fig. 24.1.

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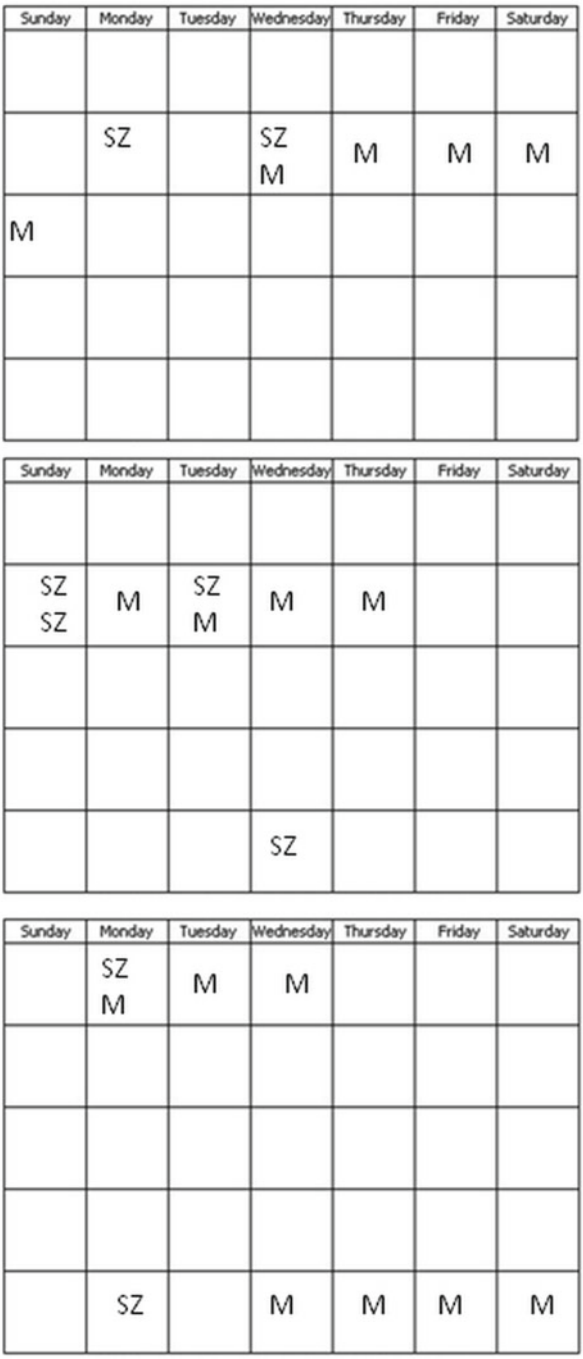
W.O. Tatum et al. (eds.), *Epilepsy Case Studies: Pearls for Patient Care*,
DOI 10.1007/978-3-319-01366-4_24, © Springer Science+Business Media New York 2014



Sunday	Monday	Tuesday	Wednesday	Thursday	Friday	Saturday
	SZ		SZ M	M	M	M
M						

Sunday	Monday	Tuesday	Wednesday	Thursday	Friday	Saturday
SZ SZ	M	SZ M	M	M		
			SZ			

Sunday	Monday	Tuesday	Wednesday	Thursday	Friday	Saturday
	SZ M	M	M			
	SZ		M	M	M	M

Fig. 24.1 Seizure calendars for 3 months demonstrating a catamenial pattern of breakthrough seizures in relationship to the menstrual cycle. *SZ* seizure, *M* menses

Clinical Questions

1. Does the diary contain information valuable to the management of this patient?
2. How does catamenial epilepsy change during perimenopause and menopause?
3. Could this patient's epilepsy have impacted her menopausal status?
4. Could hormone replacement therapy have any benefits for this patient?
5. Could hormone replacement therapy worsen her epilepsy?

Diagnostic Discussion

1. The diary demonstrates a consistent pattern of seizure exacerbation related to the menstrual cycle, known as catamenial epilepsy. When strictly defined as a doubling of seizure frequency during a specific phase of the menstrual cycle, over 30 % of women with refractory partial epilepsy have catamenial epilepsy. The most common pattern, as demonstrated in this patient's diary, is the perimenstrual pattern with increased seizures in the days immediately before (and after) the onset of menses. The influence of the menstrual cycle of seizure activity is attributed to the pro-convulsant effects of estrogen via enhancement of neuronal sensitivity to glutamate, and to the anticonvulsant effect of progesterone mediated primarily through gamma-aminobutyric acid (GABA) receptors in the brain.
2. Menopause is defined as cessation of menstrual periods for more than 1 year. This is preceded by perimenopause, which consists of several years when the menstrual cycle becomes increasingly irregular and fertility decreases due to increasingly irregular secretion of estrogen and progesterone. An increase in anovulatory cycles is encountered resulting in infertility. This patient's reporting of increasing menstrual irregularity and vasomotor symptoms (hot flashes, night sweats) are clinically consistent with perimenopause. Many women with catamenial epilepsy report worsened seizure control during perimenopause. Although cessation of ovarian production of estrogen and progesterone might be predicted to improve epilepsy after menopause, changes in seizure control after menopause are unpredictable.
3. Women with epilepsy may be at greater risk for premature menopause, defined as menopause that occurs at or before age 40. Increasing number of lifetime seizures has also been correlated with younger age at menopause. This patient's longstanding history of intractable epilepsy may have contributed to development of perimenopausal symptoms at her young age.
4. Hormone replacement therapy (HRT; estrogen or estrogen plus progesterone) is currently used to effectively treat menopause related symptoms and to prevent postmenopausal osteoporosis that may be accelerated by some ASDs placing women with epilepsy at increased risk for fractures. Vasomotor symptoms are the most common indication. Women undergoing premature menopause (age 40 years or less) are at increased risk for bone disease, and may receive greater

benefit from HRT than women developing menopause at a later age. For women with epilepsy, vasomotor symptoms that disrupt sleep can adversely impact not only quality of life, but also seizure control. When considering initiation and duration of HRT, the potential benefits to a given individual must be weighed against her personal risk profile for venous thrombosis, vascular disease, and breast cancer associated with treatment.

5. HRT could exacerbate this patient's seizures in two ways. Firstly, the hormones themselves could influence seizure threshold. A randomized, controlled trial of combined estrogen/progesterone HRT in postmenopausal women with epilepsy demonstrated increased seizure frequency in over half of those treated. Furthermore, in those women using lamotrigine, serum drug levels were lowered 25–30 % by HRT. The patient should be counseled on the potential risks of worsened seizure control related to HRT. However, these risks should be balanced against the severity of the vasomotor symptoms and the risks in an individual patient for osteoporosis. If HRT is started, AED dosing may need to be adjusted to maintain therapeutic serum drug levels.

Clinical Pearls

1. Catamenial epilepsy reflects a predictable seizure exacerbation in women with epilepsy. It is a reproducible pattern that is linked to a specific phase of the menstrual cycle and is a common feature for females with seizures and epilepsy.
2. Many women with catamenial epilepsy will note worsened seizure control during the perimenopausal time period.
3. Women with refractory epilepsy may experience menopause at a younger age.
4. Hormone replacement therapy may exacerbate seizures in women with epilepsy but may be beneficial for symptoms associated with menopause and to ensure bone health.

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Chapter 25
Seizure Versus Syncope

William O. Tatum IV

Case Presentation

A 21-year-old right-handed female presented to clinic with a diagnosis of "seizure disorder." Birth, labor, delivery, and development were normal. At 14 years of age she experienced her first "blackout." She was taken to the local Emergency Department (ED) and was diagnosed with syncope. She injured her elbow and was admitted with a normal neurological examination. Following admission, a brain MRI and laboratory testing was normal. Following her discharge, she continued to experience infrequent breakthrough events several times a year usually during stress or missed meals. She was seen by the Epilepsy service and underwent a brain MRI which was normal. An EEG demonstrated "bifrontal polyspikes that are potentially epileptogenic discharges and that are suspicious for a seizure disorder." Clinical correlation was "strongly advised." She subsequently was placed on phenytoin (PHT). A recent episode had witnessed "jerking." Higher doses of PHT titrated to 400 mg nightly resulted in mild intermittent dizziness, blurry vision, and incoordination. She eventually graduated high school with difficulty, though was unable to find employment due to transportation limitations since she did not drive. She became pregnant despite using the birth control pills and had her pregnancy terminated due to the fear of birth defects from her PHT. She was subsequently seen for another opinion.

On review of her history, "blackouts" were described as a sudden feeling of progressive dizziness, visual constriction, sweating, clammy skin, and then loss

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W.O. Tatum et al. (eds.), *Epilepsy Case Studies: Pearls for Patient Care*,
DOI 10.1007/978-3-319-01366-4_25,

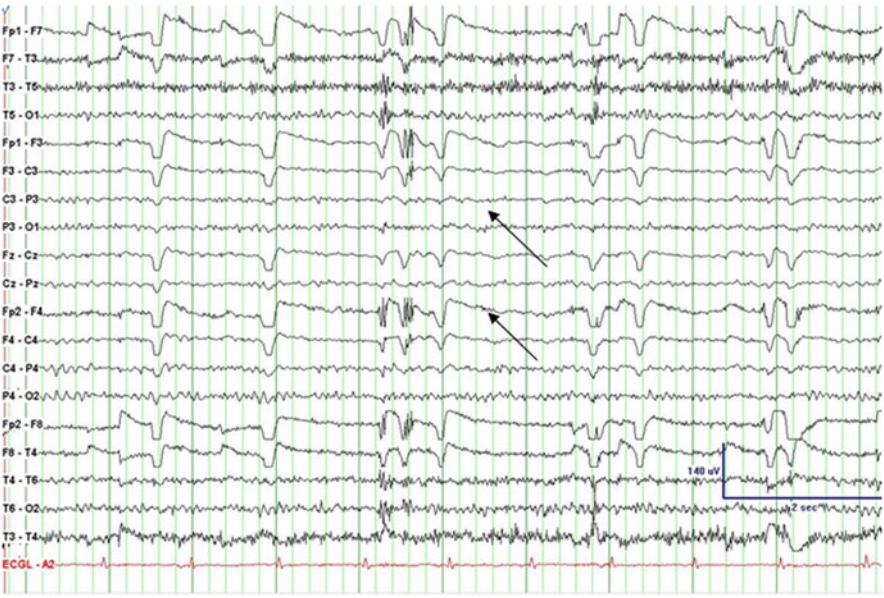

Fig. 25.1 EEG demonstrating bitemporal wicket spikes during N1 sleep. Note the bursts and spike morphology during stage 1 sleep (*arrows*). EEG parameters include a bipolar montage, sensitivity of 7 μV/mm, and filters of 1–70 Hz

of consciousness. Others would see a limp collapse and pale color. Following the collapse she would be "confused." This occurred relative to the situation, but was unassociated with post-ictal disorientation and lethargy. Her examination was normal but for minimal horizontal nystagmus. A 3-Tesla brain MRI was normal and repeat EEG in the awake through stage 2 sleep state revealed the presence of wicket waves during drowsiness and light sleep (Fig. 25.1). Despite efforts to retrieve her EEG it was unable to be obtained. Following evaluation, our patient was referred to cardiology where a tilt-table test was significant for one of her "typical blackouts." She was diagnosed with neurocardiogenic syncope.

Clinical Questions

1. What diagnosis is suggested by the clinical history?
2. What features differentiate seizure from syncope?
3. How common is "jerking" during syncope?
4. What role does the EEG have in the diagnosis of seizures and syncope?
5. What are the consequences of treatment in this patient?

Diagnostic Discussion

1. Syncope is the most common epilepsy mimic. It occurs when a brief, transient, self-limited loss of consciousness results from a global reduction of normal cerebral perfusion. Neurally mediated syncope, syncope due to orthostatic hypotension, and cardiogenic syncope are the three types of syncope. Neurally mediated syncope is the most common type affecting up to 40 % of the population. Triggers such as pain, prolonged standing, fear, coughing, toileting, and phlebotomy (our patient) are common. The features distinguishing seizures from syncope are listed in the table. Prodromal features of dizziness (light-headedness) typically occur. Associated features of visual constriction, nausea, pallor, heat or chills, and diaphoresis are common. When standing or sitting the head is approximately 25–30 cm above the heart. Arrest of cerebral blood flow normally takes <10 s before consciousness is impaired and then lost. During this time the EEG becomes initially slow and then flat. As a fall or lying down takes place, resumption of cerebral perfusion occurs and consciousness is regained unless other etiologies exist. Like most patients with non-epileptic events, a 7-year period was present before her definitive diagnosis. History is the cornerstone to achieving the correct diagnosis.
2. The features that distinguish syncope from seizures are listed in Table 25.1. The symptoms at onset with seizures include an aura often consisting of deja vu or an indescribable sensation rather than dizziness. An abrupt loss of consciousness with seizures is associated with excess motor signs (tonic posturing or clonic jerking). In syncope, there is a loss of motor integrity (limp collapse). When syncope is prolonged and reduced cerebral blood flow is maintained (in this case due to upright seated position) then multifocal myoclonus or a few clonic jerks is seen in most normal individuals. The characteristic post-ictal disorientation and encephalopathy noted following a seizure, in those with syncope is absent except for confusion regarding unexpected loss of consciousness. Urinary incontinence and injury may occur in both. These are related to the unconscious state

Table 25.1 The clinical features of syncope and seizures

Clinical	Syncope	Seizure
Triggers	Present	Rare
Out of sleep	No	Yes
Onset	Nausea and sweating	Déjà vu or ictal fear
Movements	Myoclonic, tonic, clonic <15 s	Sustained tonic or clonic
Coloration	Pallor	Cyanosis
Post-ictal	No	Yes
Myalgias	Rare	Common
Incontinence	Maybe	Maybe
EEG during event	Abnormal-non-epileptiform	Abnormal-epileptiform

and not the pathophysiology. Electrocardiographic monitoring and echocardiography are frequently more valuable "tests" in syncope than an EEG. Head-up tilt-table testing may be diagnostic.

3. Myoclonus, clonic jerks, or tonic posturing commonly occurs in up to 90 % of normal individuals that experience syncope. When convulsive syncope occurs, it bears no relationship to epilepsy. In epilepsy the jerks can begin unilaterally. They may subsequently become bilateral, high-amplitude, rhythmic, and synchronous clonic jerks that may lead to visible flexion of the joints as they become "violent." Convulsive syncope on the other hand has an initial atonic portion of the event that is subsequently noted to have multifocal myoclonic jerks or slow tonic posturing that is distinguished from the sequence of tonic–clonic motor involvement seen with seizures. Rarely, epileptic seizures may cause syncope through bradycardia or asystole. In hospitalized patients undergoing video-EEG telemetry monitoring this has comprised approximately <0.5 % of monitored patients. There have been a few patients in whom epileptic seizures occurred as a result of neurally mediated syncope.
4. This case is an excellent example of the ramifications that may occur from a misinterpreted EEG. When used as a means of diagnosis it is often fraught with misleading information that is interpreter-specific. Our patient was initially believed to have a clinical diagnosis of syncope by her attending physician. However, following the EEG the diagnosis was changed to a diagnosis of seizure disorder. Subsequently it was determined that artifact was superimposed on eye blink artifact creating the "potentially epileptogenic" waveforms that had been seen in the past. Artifact and normal variants are the most common reasons for a misinterpreted EEG. The EEG in our patient was normal without evidence to support the diagnosis of epilepsy. Some waveforms and combinations of normal and artifactual waveforms mimic pathological epileptiform discharges. While an interictal EEG is not necessary in a case of clear syncope, if the event is not witnessed or unclear, then ictal recordings may be required to differentiate the two events. Similar to the presence of motor movements seen in epilepsy, the EEG shows "positive" features with epileptiform discharges. The flaccid collapse in concert with the flattening of electrocerebral activity on the EEG reflects the "negative" features of syncope.
5. PHT is a poor choice in this patient. First and foremost because she does not have epilepsy. PHT will confer no benefit of treatment and as a result of treatment she experienced consequences from both her diagnosis (unable to drive and work) and treatment (unplanned pregnancy) that significantly complicated her life. In this case compromise of the efficacy of our patient's oral contraceptive pill likely lead to an unexpected pregnancy. Because PHT has been associated with teratogenesis that was feared by the patient, a termination of pregnancy was sought and undertaken with the potential for lifelong psychological ramifications as a "side-effect" of treatment. Cardiology subsequently supported a diagnosis of syncope, she was encouraged to drink fluids and a liberal salt diet was advised. Recommendation for behavioral avoidance of precipitating activities was also

advised. She was slowly tapered from PHT without ill-effect and has remained without worsening of her clinical condition 2 years after diagnosis.

Clinical Pearls

1. Neurally mediated syncope is very common in the general population. It is the most common cause of physiologic non-epileptic events.
2. The presence of a trigger, prodromal symptoms of dizziness, autonomic symptoms, limp collapse that is devoid of clear post-ictal disorientation, confusion, and lethargy are common symptoms of syncope. In contrast epileptic seizures typically occur spontaneously or directly out of sleep, may be associated with an aura, automatisms, and tonic posturing or rhythmic clonic jerking, followed by a post-ictal state.
3. EEG is less useful in syncope when the history clearly suggests syncope. Wicket spikes are the most commonly misread EEG pattern due to their appearance. Artifact is one of the pitfalls that may lead to an overinterpretation of the EEG and an overtreatment of epilepsy.
4. Head-up tilt table testing is a more appropriate test used in the diagnosis of syncope, in association with a thorough cardiology assessment. Fluid and salt are often recommended. Antiseizure drugs have no role in the treatment of syncope or convulsive syncope.

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Chapter 26
Dementia and Seizures

William O. Tatum IV

Case Presentation

A 64-year-old right-handed Caucasian female developed an insidious onset of progressive difficulties with her memory. Early spells of visual distortion were noted where she said her vision would "seizure up." Memory rapidly deteriorated as visual loss progressed. She was unable to remember daily activities, though it fluctuated from day to day. She became unable to keep her appointments and began pulling away from contact with her family. Her daughters became concerned and increased the level of family supervision 4–5 months later. Personality changes then became notable. She became less outgoing, more apathetic and withdrawn, and was less gregarious than her "typical self." Mobility problems interceded and she began to complain of balance issues. She deteriorated to the point where she would be "found down" requiring frequent assistance from others. She was seen by neurology and diagnosed with Alzheimer's disease (AD) but failed to improve despite donepezil. Concerns for seizures were raised and she was referred for assessment. On evaluation, she was seated in a wheelchair and withdrawn with limited spontaneous interaction. Impairment in memory, visual fixation and pursuit, rapid alternating movements, and gait ataxia was evident. A brain CT was normal. A routine EEG is presented in Fig. 26.1. MRI was pending.

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W.O. Tatum et al. (eds.), *Epilepsy Case Studies: Pearls for Patient Care*,
DOI 10.1007/978-3-319-01366-4_26,

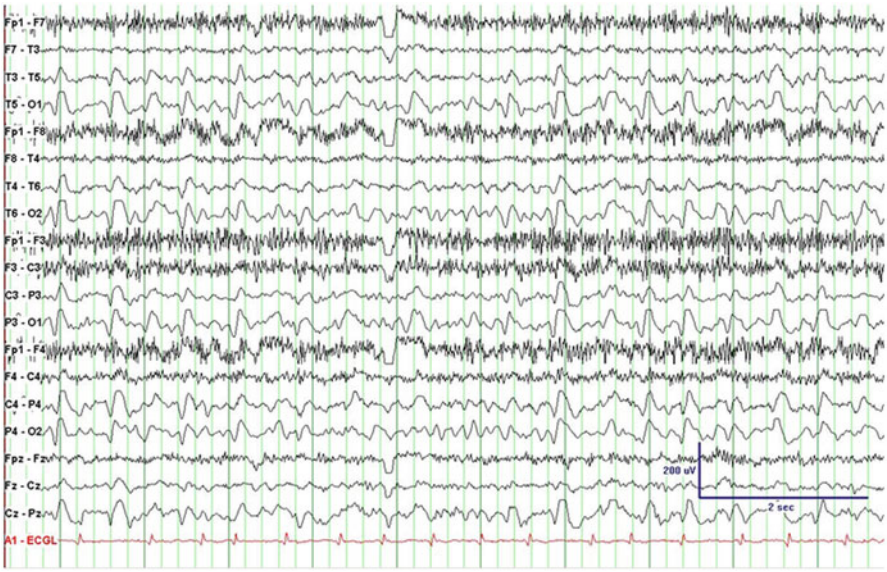

Fig. 26.1 EEG demonstrating bilateral periodic occipital sharp-and-slow wave complexes with a repetition frequency of 1–2 Hz. EEG obtained utilizing a longitudinal bipolar montage. Parameters of recording included a sensitivity 10 μV and filter settings of 1–70 Hz

Clinical Questions

1. What is her primary problem?
2. How does the EEG support a particular clinical diagnosis?
3. What is the association between seizures and dementia?
4. What treatments are there for this patient?
5. What is the anticipated clinical course and prognosis?

Diagnostic Discussion

1. An insidious onset of progressive recent memory decline suggests dementia is her primary problem. Dementia is a global loss of previously obtained cognitive function. AD affects 50–60 % of all cases and is associated with seizures in 10–22 %. Up to 35–50 % of patients living to age 85 years will manifest changes suggesting AD. However, in this case the rapid progression of the dementia is notable. Prion disease is an uncommon group of neurodegenerative disorders characterized by rapidly progressive dementia. Creutzfeldt–Jakob disease (CJD) is the most common form of this transmissible spongiform encephalopathy

caused by an accumulation of an abnormal isoform of host-encoded cellular prion protein. Several variants exist. In our patient, the presence of early visual dysfunction and rapidly progressive neurodegeneration involving memory and cognition is characteristic of the Heidenhain variant of CJD due to involvement of the occipital cortex.

2. The EEG demonstrates surface negative periodic bioccipital symmetric synchronous potentials recurring at 1.5 Hz. According to Steinhoff, in CJD the periodic complexes occur with a sensitivity of 61 % but a specificity of 91 %. Their positive predictive value is 95 % when found in the right clinical setting. A negative predictive value of 49 % has been found and, when present, 3 month course may suggest familial or variant forms of the disease where the periodic discharges are less commonly present. As the duration of the disease continues, complexes may become multiphasic and complex. The predilection for the occipital lobe suggests the Heidenhain variant. However, sharply contoured waveforms and triphasic waves may occur over the posterior head regions in severely demented patients without CJD. Epileptic seizures occur in dementia at a higher prevalence than in normal elderly people. Even though the periodic potentials are epileptiform in morphology, they represent an epiphenomenon of the infectious-inflammatory process and not an epileptiform discharge associated with seizures.
3. Seizures are increased in patients with dementia, though the incidence varies with the specific etiology. When memory disturbances exist in the absence of other deficits of cognition, Mild Cognitive Impairment has a risk of 15 % per year of developing dementia. AD is associated with seizures. Furthermore, seizures are a common comorbidity in those with early onset AD. These are typically focal seizures with the semiology demonstrating less motor involvement with advancing age. When seizures are subtle, nocturnal, or occur in seniors that expect memory loss, the diagnosis may be elusive. If memory loss fluctuates, subtle temporal lobe seizures without awareness should be considered. Stroke is the most common identifiable cause of epileptic seizures in the older population. Nearly 10 % of patients suffering a stroke will manifest seizures, with a greater risk when the stroke is hemorrhagic.
4. Providing a definitive diagnosis is perhaps the best “treatment” to allow family members and the patient the resolve of a future understanding in dementia. Genetic testing is available for early-onset autosomal dominant AD. Neurodegeneration may benefit from cholinesterase inhibitors and memantine, and vascular dementias require stroke prevention in addition. When seizures develop, excluding a symptomatic cause is key. Most patients after a first seizure will require antiseizure drugs with dementia due to the symptomatic etiology. Selecting drugs with minimal effects on cognition and drug–drug interactions in the lowest possible dose is essential. Levetiracetam, lamotrigine, and gabapentin are particularly useful in the elderly. Valproate and carbamazepine may be used, but carry a greater likelihood of adverse effects. Normal pressure hydrocephalus may respond to shunting and is diagnosed by high-volume lumbar puncture. Cerebrospinal fluid analysis demonstrating low beta amyloid 1–42 and high T-tau and P-tau may provide high sensitivity and specificity of AD. An elevated 14-3-3 protein when pres-

ent suggests prion disease. In our patient, the brain MRI demonstrated a high signal lesion affecting the cortical ribbon of the posterior cortex on DWI sequences that strongly suggested CJD. In the face of the clinical course and EEG findings this suggested the Heidenhain variant of CJD. Treatment with ASDs is not indicated despite the EEG findings. At first the periodic potentials may suggest an electrographic seizure, though no semiology is coupled with it and no evolution is present on the EEG to suggest an electrographic seizure. Benzodiazepines may have a transient nonspecific effect in eliminating the potentials on the EEG. There is no effective treatment. Supportive care, physical therapy, social services, and symptomatic relief of insomnia, agitation, and anxiety are important adjuncts to address.

5. The prognosis is poor. With progression of the disease, hospice and hospital services become important. Death typically occurs in months, though up to a few years may pass from the onset of symptoms. Genetic counseling is important if a familial basis is suspected. Prion diseases are reportable entities to the public health services. Autopsy can confirm the disease process and, given the tragic results, provide insight into the surveillance of the disease.

Clinical Pearls

1. Dementia is a major health concern with seizures occurring in demented elderly to a greater extent than the general healthy population.
2. Rapidly progressive dementias associated with prion disease are rare. They may have periodic patterns on EEG that are characteristic of the disease, yet do not implicate seizures in the diagnosis or treatment.
3. Of the dementias that exist, few are treatable with disease-modifying agents. It is important to exclude treatable causes such as structural etiologies, normal pressure hydrocephalus, and drug-induced delirium, though AD is the most common cause.
4. Selecting ASDs that have minimal effects upon cognition and few drug–drug interactions are crucial to preserve memory function and limit cumulative toxicity from medication in this age group.

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Chapter 27
Video-EEG Monitoring and Reflex Epilepsy

Joseph Drazkowski

Case Presentation

A 21-year-old right-handed male college student was evaluated for a 2-year history of spells that occurred primarily while reading text books. He grew up with an abusive father who was an alcoholic. Risk factors for seizures included multiple concussions while playing high school football. The attacks were frequent and severe enough to cause him to leave school when they would occur. His professors and school officials thought he was making the events up to avoid school. During the events he was described as abruptly staring off into space with unresponsiveness that would last for several minutes. His family stated he may have had a rare event even when he was not reading. The events were so disruptive that he contemplated leaving school permanently. There was no history of injury from the events, nor was there an aura or history of a convulsion. He is mildly anxious and depressed. He smoked marijuana, which he thought helped these events. His neurological examination was normal. Two routine sleep deprived EEG's (with photic stimulation and hyperventilation) and a high-resolution brain MRI with attention to the temporal lobes were normal. Video-EEG monitoring was performed. Two events were captured (Fig. 27.1). Both occurred while reading an anthropology text book. EEG demonstrated an abrupt run of independent bi-temporal rhythmic ictal theta activity provoked by reading. SISCOM imaging correlated with EEG during his right temporal seizure. PET scan and neuropsychological testing were non-localizing. Subsequently, the patient failed to respond to four ASDs. Invasive EEG recording was performed in the course of pursuing resective epilepsy surgery.

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W.O. Tatum et al. (eds.), *Epilepsy Case Studies: Pearls for Patient Care*,
DOI 10.1007/978-3-319-01366-4_27, © Springer Science+Business Media New York 2014

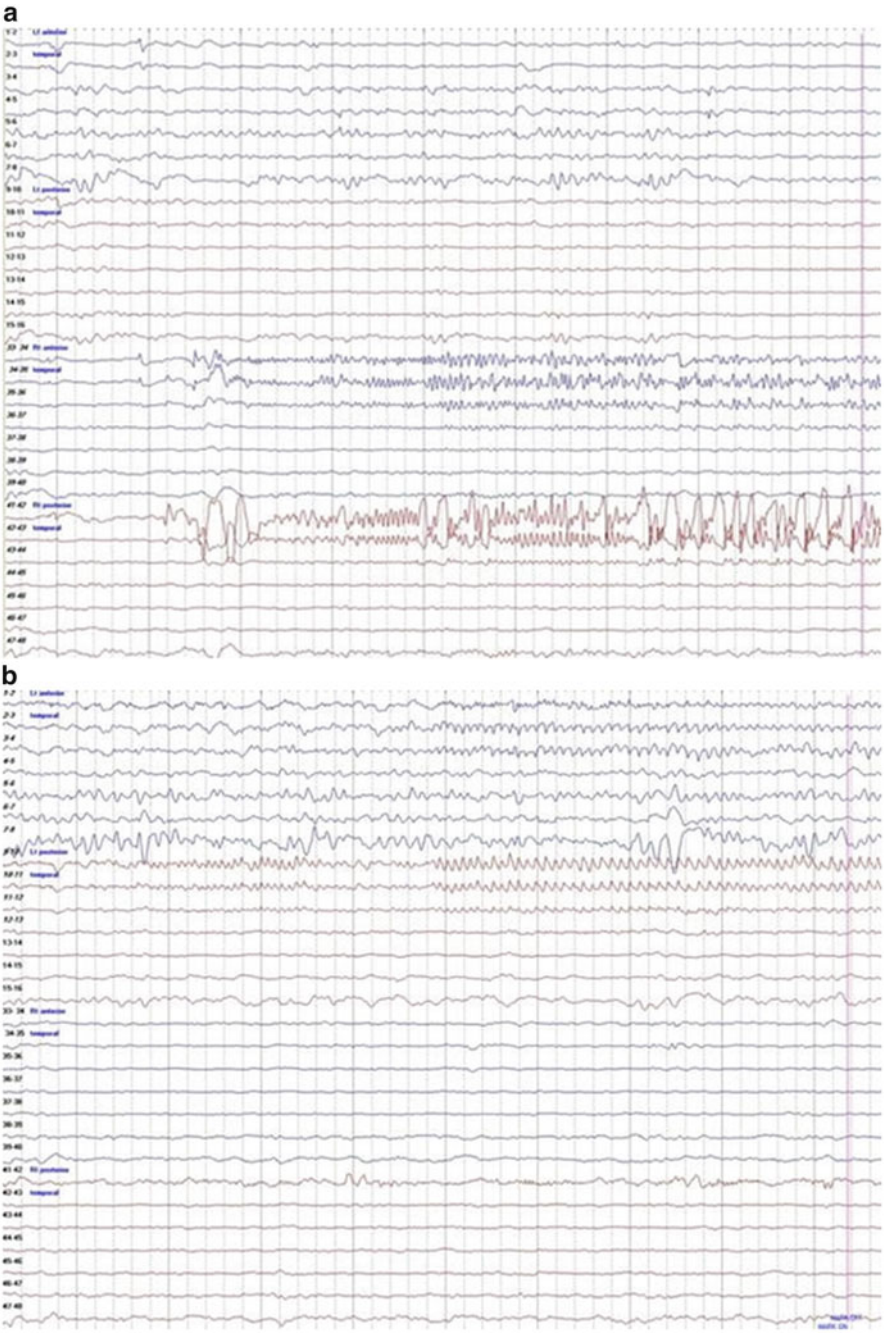

Fig. 27.1 (**a**) Depicts electrographic seizure onset from the deep contacts of the right temporal depth electrodes (hippocampus and amygdala). (**b**) Depicts another morphologically distinct electrographic seizure onset in the deep contacts of the left temporal electrodes (hippocampus and amygdala)

Clinical Questions

1. What type of epilepsy does this patient have?
2. What is the likelihood another seizure drug will provide seizure freedom?
3. What is the most effective treatment for drug-resistant localization related epilepsy patients?
4. Given the phase II EEG findings, what is the likelihood that resection will provide acceptable outcome in seizure control?
5. What are other treatment alternatives to resective surgery and medications for this patient?

Diagnostic Discussion

1. In this case, video-EEG was diagnostic of electroclinical focal seizures triggered by reading. The use of intracranial EEG with depth electrodes then confirmed independent bi-temporal seizures. A single focus amenable to resection was, unfortunately, not present to pursue surgical therapy. A somewhat unusual component of the history is that the seizures were reflexively provoked by reading. Reflex epilepsy is rare when the stimulus is the sole means of seizure activation. Seizures due to photic stimulation are the most common form of reflex epilepsy, though triggers may be very unique or individualized such as our patient with reading epilepsy. The circumstances in this case raised the possibility of a secondary gain (because he was leaving school). An initial evaluation with EEG was unrevealing and frustrated the patient and school officials due to a lack of definitive diagnosis emphasizing that routine EEG may be insufficient unless event-recording is obtained.
2. In cases where more than two ASDs have failed to control epileptic seizures, the probability that further antiseizure drugs will render the patient seizure-free is greatly reduced with further trials (see case on refractory epilepsy). Treatment in cases of the reflex epilepsies focus on behavioral modification and stimulus avoidance. In this case, the act of reading had impractical ramification of avoidance in a young patient's educational achievement and could not be avoided. Maintaining regular sleep, nutrition, and compliance with ASDs, in addition to eliminating drugs and alcohol from his activities, was a cornerstone to physician recommendations.
3. When ASDs fail to control seizures, resective surgery should be considered. A comprehensive surgical evaluation to determine if the patient will benefit from a surgical approach is needed. A tertiary level epilepsy center capable of performing invasive EEG is necessary. Invasive EEG is often considered when non-lesional focal seizures do not have a clear onset delineated.
4. Independent bi-temporal seizure onset was confirmed in our patient through the utilization of invasive EEG. Unless a clear predisposition is evident to suggest

unifocal epilepsy, bilateral independent seizures predict a poor outcome from resective epilepsy surgery. Improved quality of life measures, after resective epilepsy surgery, depend upon the patient remaining seizure-free. Seizure freedom allows for the person with epilepsy to more fully participate in important life activities such as school, work, and driving.

5. When a patient is not an appropriate surgical candidate, there continue to be options. Many new ASDs are available now or are being released that may provide a small but real chance of seizure control or more likely seizure reduction. Additionally, the ketogenic diet (see case), investigational ASDs, and neurostimulation are also available for use. Currently, there is only one device that is approved by the FDA for use in people with epilepsy in the USA. This device is the vagus nerve stimulator (VNS), which has been shown to be safe and effective in the treatment of chronic epilepsy. Recent trials involving implanted electronic devices have been undertaken. Two trials have involved neurostimulation. One paradigm has been employed that uses stimulation in response to recorded abnormal EEG (responsive neurostimulator; RNS). The other involves surgically implanted deep brain stimulation (DBS) utilizing intracortical electrodes that stimulate the anterior nucleus of the thalamus. In our case, given the low likelihood of seizure freedom with resective surgery, the patient opted to enter a clinical trial involving the RNS. Permanent depth electrodes were placed into both temporal lobes. After training the device software "intelligence" to recognize seizures, an electrical stimulation was able to be delivered to the implanted electrodes upon seizure detection for treatment. The patient achieved excellent control of the generalized seizures and experienced a significant reduction in the number and severity of his focal seizures. The RNS is currently an investigational device that is presently under review by the US Food and Drug Administration.

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Chapter 28
Violence and Epilepsy

Jerry J. Shih

Case Presentation

A 16-year-old right-handed male with a 1-year history of aggressive behavior associated with coprolalia was seen for a second opinion regarding possible seizures. He was diagnosed with complex-partial seizures starting at age 6. During his seizure he would appear to be pointing at people with his hands. This was followed by flailing movements of the arms for brief periods of time followed by post-event fatigue and amnesia. He was suspected to have focal seizures, though a behavioral disorder was also considered. Carbamazepine was begun, which led to complete resolution of the episodes. He remained in control of the attacks and medication was withdrawn at age 9. He was well until 14 years of age when he began having brief episodes of uttering profanities while he would point at people. Seizures were considered, though he was tried on lamotrigine without success. Video-EEG monitoring was performed at age 15 (Fig. 28.1). During the monitoring session, multiple episodes were captured, though none were associated with any EEG changes. He was felt to manifest motor tics with coprolalia and was diagnosed with Tourette's syndrome. Clonidine was ineffective. A brain MRI was normal, as was a complete neurological examination. He had an episode at school in which he cursed and made threatening gestures to his teacher. She described his movements as though he was holding a gun. He was suspended from school and brought by his parents for a second opinion. A diagnostic study was performed.

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W.O. Tatum et al. (eds.), *Epilepsy Case Studies: Pearls for Patient Care*,
DOI 10.1007/978-3-319-01366-4_28, © Springer Science+Business Media New York 2014

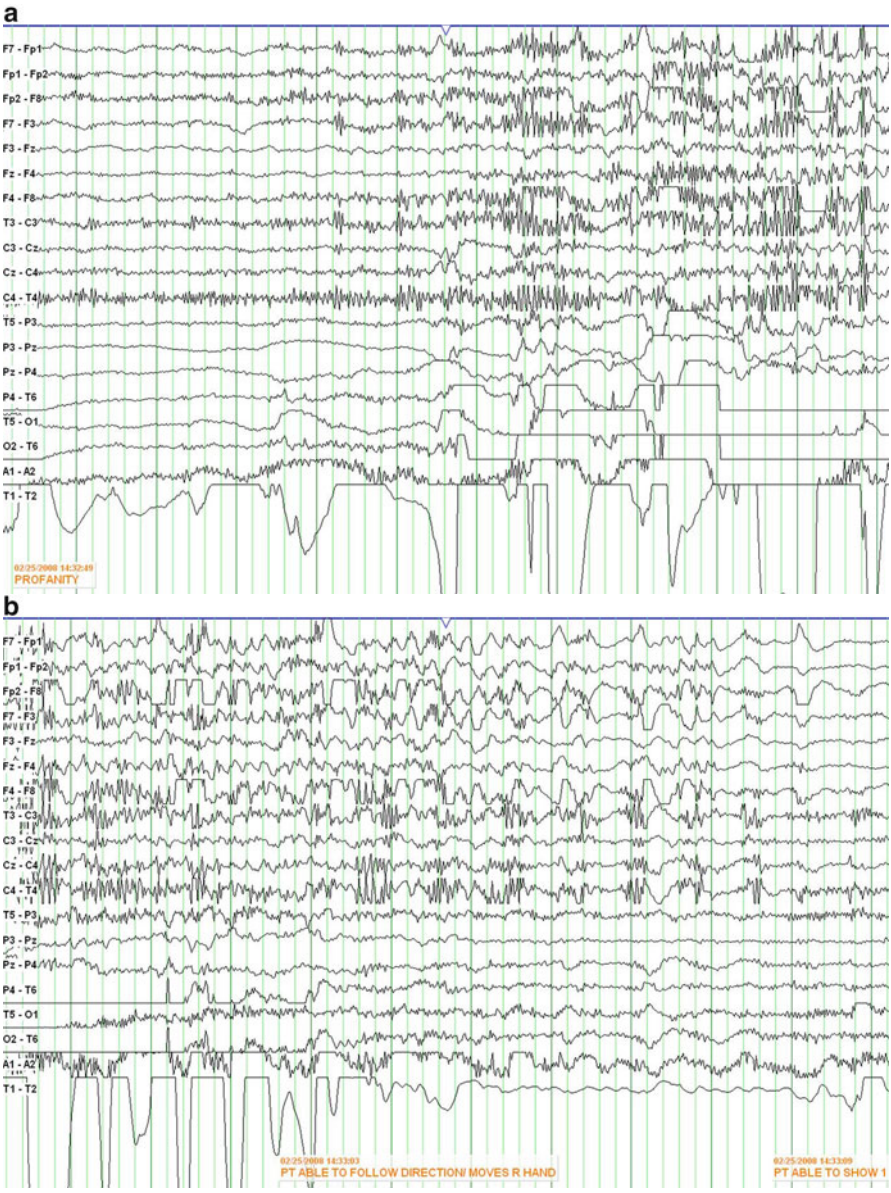

Fig. 28.1 (**a**) and (**b**): Video-EEG demonstrating an evolving frontal rhythmic ictal discharge during an "episode" where he was cursing and appeared to be shooting a handgun

Clinical Questions

1. How does the video-EEG help support the diagnosis?
2. What other testing may be helpful to confirm the diagnosis?
3. What is the pathophysiology underlying this behavior?
4. What is the best course of treatment?
5. What safeguards and precautions should be exercised with this patient?

Diagnostic Discussion

1. Video-EEG monitoring is the gold standard to provide a definitive diagnosis of epileptic seizures. The presence of an electrographic ictal change during a habitual "episode" within the right clinical context is diagnostic of a seizure. Bizarre seizures may be confused with behavioral events, yet the brief duration is a clue to the diagnosis of epilepsy. The EEG portion of the recording (Fig. 28.1) demonstrates a condensed transverse bipolar montage that accentuates the frontal regions of the head. The EEG in our patient demonstrated an evolving bifrontal 5–6-Hz rhythmic ictal theta frequency that correlated with his behavioral changes confirming the diagnosis of epilepsy. The electroclinical localization was characteristic for seizures associated with frontal lobe epilepsy (FLE).
2. Seizures that are very brief or those with prominent (hypermotor) movement may limit the ability of scalp EEG to detect changes, even during a seizure in FLE. Although ictal SPECT is most commonly used to help localize an epileptogenic zone, the test is occasionally used to help confirm a seizure diagnosis, especially in cases of focal seizures without impaired consciousness (simple partial seizures) or with brief durations and impaired consciousness (FLE). Our patient had an ictal SPECT that demonstrated increased regional hyperperfusion in the right lateral and orbitofrontal cortex reflecting an increased blood flow from the greater metabolic demand imposed by the seizure.
3. More so than seizures arising from other brain locations, frontal lobe seizures may exhibit bizarre and unusual behaviors. Extratemporal seizures are often brief and are associated with bizarre nonconvulsive behaviors that may be misinterpreted as behavioral disorders or psychogenic non-epileptic attacks (pseudoseizures) by virtue of their ability to vocalize or curse (seen in 30 % of patients with FLE). Well-organized, purposeful, complex, goal-directed behavior is highly unlikely during a seizure. This patient is an unusual case demonstrating ictal aggressive behavior with complex motor and vocal features that was misinterpreted to be a goal-directed violent action. The pathophysiology of this behavior is likely related to activation of circuitry in the primary somatomotor and premotor cortex that is connected with higher psychic function as well as limbic regions.
4. The best course of treatment is to control the seizures by providing a definitive diagnosis and employing optimal antiepileptic drug therapy. Not every patient

will respond to the same ASDs. In this patient's case, he had responded very well to carbamazepine at a younger age. A retrial of carbamazepine was instituted and the patient again became seizure free. Apparent acts of violence may occur in patients with epilepsy during the postictal state. Appearing as an expression of unconscious resistive violence, aggressive resistance may occur to thwart the attempts of would-be helpers to prevent the individual from performing injurious activities. An evaluation for resective epilepsy surgery is indicated when the patient continues to have debilitating seizures despite appropriate treatment with at least two first-line antiseizure drugs.

5. In this patient's case, every effort should be made to openly communicate with his teachers, colleagues, and fellow students so as to minimize misunderstanding and potential over-reaction. Guns and hunting weapons should be kept in a locked location. When a cluster of seizures has occurred, a postictal psychosis may result. This usually has a delayed onset and may require a short course of antipsychotic medication. This condition is not uncommon during video-EEG monitoring where cluster seizures commonly occur.

Clinical Pearls

1. Patients with FLE may exhibit bizarre and unusual behavior such as vocalizations, hyperkinetic gestures, and complex movements that can be mistaken for psychogenic non-epileptic events.
2. The diagnosis of seizures should always be considered in cases of brief episodic stereotyped behavior.
3. In potential cases of FLE, even ictal EEG may be misleading when an electrographic correlate is not visualized and a brain MRI fails to disclose a lesion. In that case, ancillary testing with ictal SPECT may be helpful in supporting a clinical diagnosis of FLE.
4. Goal-directed violence during an epileptic seizure is rare.
5. Protecting others as well as the patient should include safe-guarding the home and reinforcing seizure precautions.

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Chapter 29
Psychogenic Nonepileptic Seizures

William O. Tatum IV

Case Presentation

A 33-year-old right-handed female had obstructive sleep apnea, depression, fibromyalgia, and mitral valve prolapse, and was being evaluated for chronic fatigue. Her only surgery was a successful gastric bypass. She was otherwise in a state of usual health when she became involved in a motor vehicle accident (MVA) and subsequently began having seizures. No early risk factors were noted and her MVA had resulted in a minor head injury but no loss of consciousness. Her initial spell occurred when she was at home visiting her parents after a recent divorce. She was seated on the couch and suddenly "started shaking all over." It lasted for about 5 min, by her parents' report, and she was tired and sore after the event. She was seen at the local emergency room and loaded with phenytoin (PHT). A brain CT, a 12-lead EKG, and electrolytes were normal. She was released and complained of "feeling drunk" on PHT. Recurrent episodes occurred within the week and increased to daily episodes without response to medication. She was seen by a neurologist and begun on levetiracetam (LEV). An EEG was reported to be abnormal showing "bilateral spike discharges that are potentially epileptogenic." On LEV, the episodes continued but her parents noted that she became very depressed. They "had to" help care for her two children as she became "nonfunctional" due to her seizures. She was encouraged to seek the help of psychiatry and her parents suggested that she get another opinion. When evaluated, her father brought in a smart phone video of one of the events. She was admitted and discontinued from LEV when wicket spikes and psychogenic non-epileptic seizures (PNES) were captured. Her abnormal EEG is below (Fig. 29.1).

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W.O. Tatum et al. (eds.), *Epilepsy Case Studies: Pearls for Patient Care*,
DOI 10.1007/978-3-319-01366-4_29,

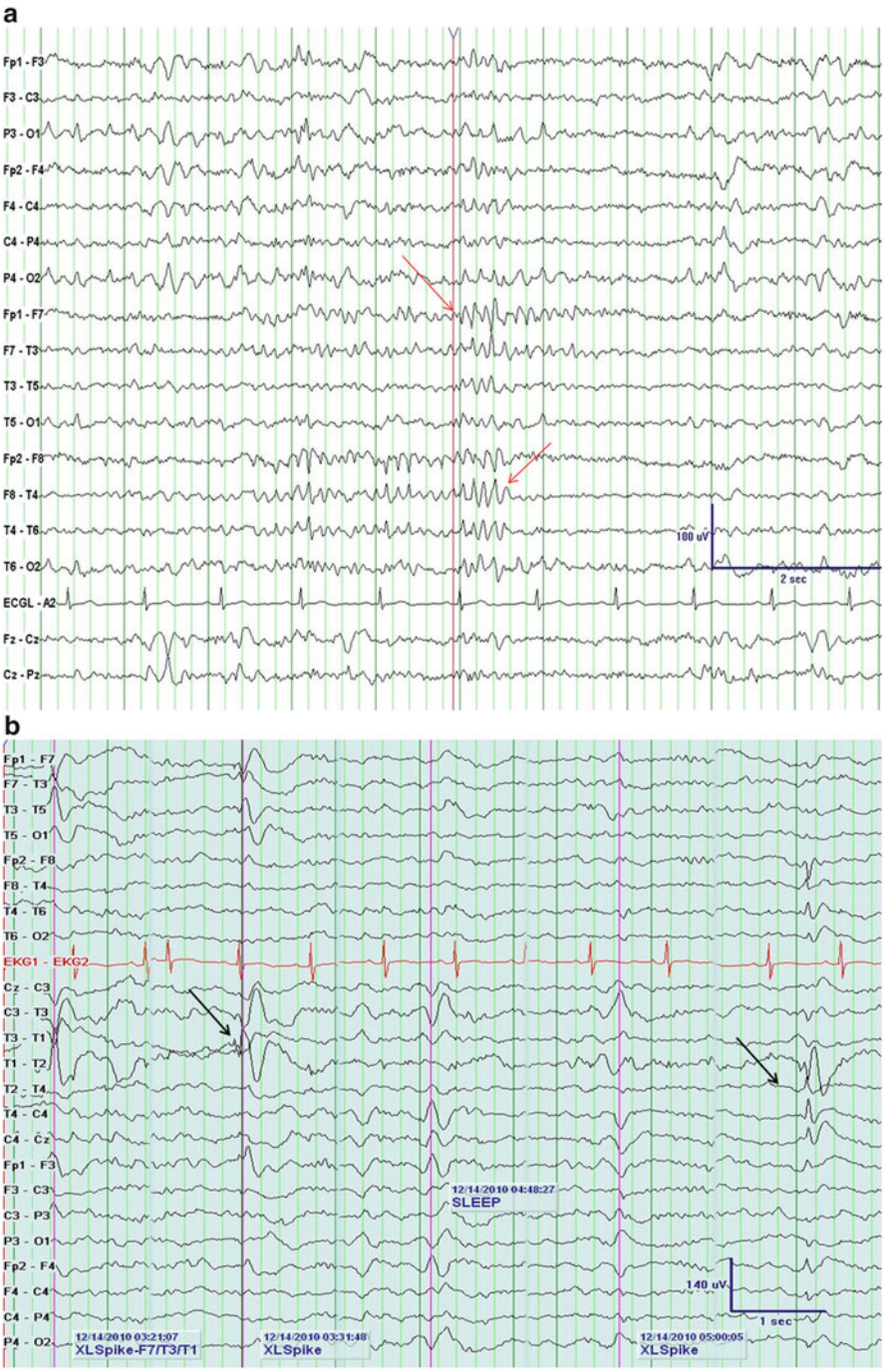

Fig. 29.1 EEG (**a**) demonstrating bilateral wicket spikes (*red arrows*) and (**b**) pathological spike-and-slow-waves in the temporal regions (*black arrows*)

Clinical Questions

1. What does the history suggest as a diagnosis?
2. What are the implications of the EEG?
3. How often is a diagnosis of epilepsy disproven?
4. What is the treatment for PNES?
5. What is the prognosis?

Diagnostic Discussion

1. The history of paroxysmal events with loss of consciousness and post-event fatigue is suspicious for the diagnosis of epilepsy, especially with an abnormal epileptiform EEG. However, the history of depression, fibromyalgia, and mitral valve prolapse have been associated with the psychological conditions of anxiety and disordered mood. The trigger by a minor head injury, without loss of consciousness, and MVA in the face of social unrest sets the stage for developing non-epileptic events. The episodes themselves were frequent, without any response to ASDs. The main differences between PNES and ES are listed in Table 29.1.
2. While the sensitivity of an EEG in patients with epilepsy is low to moderate, the specificity of an epileptiform EEG in patients with paroxysmal behavior suggesting seizures is very high. Only 1–2 % of patients will have abnormal interictal epileptiform discharges and no evidence of epilepsy. However, there are many variations of normal and variants of uncertain significance that may mimic pathological epileptiform discharges leading to misdiagnosis. Wicket waves, in this case, were noted upon recovery of the "abnormal" EEG. This is likely a common occurrence in epilepsy centers and reflects the level of experience and training of the reader. These waveforms, perhaps the most commonly misinterpreted "normal variant," consist of intermittent bursts or sporadic monophasic arciform waveforms that may be mistaken for an abnormal temporal spike. However wickets are not associated with aftergoing slow waves, do not distort the background activity, and have a similar frequency with adjacent waveforms.

Table 29.1 The clinical features of psychogenic non-epileptic seizures and epilepsy

Feature	PNES	Epilepsy
Age involved	15–35 years	All ages
Seizure onset	Gradual	Abrupt
Population	80 % Female	Male = female
Semiology	Non-stereotyped: Eyes closed	Stereotyped: Eyes open
Duration	Prolonged > 2–3 min	Usually < 1–2 min
Postictal	Rare and variable	Yes — somnolent
Injury	Infrequent, usually mild	Tongue biting and injury/burns
Activation	Reliable	Rare
EEG	Normal	Abnormal

3. On average, 20–30 % of patients (range 10–50 %) will have a different diagnosis other than epilepsy when evaluated by an epileptologist and completing video-EEG monitoring. Video-EEG monitoring is the gold standard for the diagnosis of non-epileptic events. Ninety percent of these non-epileptic events will be due to a psychogenic cause. Induction with placebos has demonstrated suggestibility associated with psychogenic etiologies. Ten percent of the time, physiologic episodes (predominately syncope) will be present. The diagnosis hinges on recording the typical event with a normal or an unchanged ictal EEG. When consciousness is impaired, the EEG will exhibit changes that quickly reflect the loss of cerebral blood flow with slowing and attenuation of the background rhythms to the point of a "flat" recording. It is during this time that multifocal myoclonic jerks or tonic stiffening may appear and mimic seizure behavior. This is known as convulsive syncope and has characteristic features that differentiate it from a generalized tonic-clonic seizure.
4. The treatment of PNES begins with the delivery of the diagnosis. The way patients react to a diagnosis of psychological cause predicts how well they will follow recommendations and, ultimately, the overall benefit of realizing such a diagnosis. It is important to present the diagnosis with a strong and positive position of recognizing a new diagnosis. PNES reflect a conversion disorder with seizures that are mimics of epilepsy, not purposely feigned. In fact, many patients may be disabled by their "seizures" and unable to control them. Pseudostatus epilepticus may occur in approximately 1/3rd of individuals. Identifying a mental health practitioner experienced in the treatment of PNES is crucial to providing a bridge between neurology and psychiatric management. Antidepressants are helpful for depression but have limited impact on resolution of the episodic behavior. Cognitive behavioral therapy, tailored to the individual needs by psychology, is emerging as the treatment of choice that may lead to reduction of the events.
5. The prognosis for patients with PNES is variable. Children have a much better likelihood of remission than adults. Like adolescents, they have different stressors than adults and may have their episodes for a shorter period of time. Most PNES diagnoses are delayed>7 years. Prolonged outcomes suggest that, after years of PNES, nearly 50 % of patients continue to have the attacks despite a definitive diagnosis. Furthermore, many are not working and reliant on social security disability. Outcome may be better in those with greater levels of education, with less severe motor involvement (1/3rd of patients may have "atonic" spells), with shorter times to diagnosis, with less somatoform complaints, and that lack significant psychiatric diagnoses.

Clinical Pearls

1. PNES is extremely common and accounts for approximately 20–30 % of hospitalizations for uncontrolled seizures. Video-EEG monitoring is the gold standard for diagnosis and notable delays are evident prior to definitive diagnosis.

2. Abnormal EEGs should be reviewed when there is the clinical suspicion that concomitant epilepsy does not exist. When waveforms are reviewed variations of normal and normal variants of uncertain significance account for the majority of misinterpreted EEGs that result in treatment.
3. The attacks themselves are a conversion disorder where patients are unaware and are without psychological "intent" to be disabled or to "fake" the seizure-like activity. Their quality of life is impaired with loss of employment and disability and many patients may continue to have events despite a correct diagnosis. The opportunity for remission starts at delivery of the diagnosis.
4. Psychiatry should seek to identify a primary psychiatric diagnosis or stressors with the purpose of considering treatment (or not) for a condition that may be comorbid with the events. Psychology that is trained in cognitive behavioral therapy may lead to reduction in the events when patients accept the diagnosis and comply with treatment recommendations.

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Chapter 30
Physiologic Nonepileptic Events

William O. Tatum IV

Case Presentation

A 58-year-old male with hypertension and hypercholesterolemia awoke one morning with a feeling that "everything was spinning" when he sat up to dress. The sensation increased with head movement and was associated with nausea and diaphoresis. He remained awake and was oriented but "woozy." He called for help and was able to adequately describe his problem. Later in the emergency department, he was diagnosed with vertigo but was admitted due to concerns about stroke. He described accidentally striking his head during yard work 2 weeks earlier. Cardiology evaluated him but found no underlying cardiogenic etiology or evidence of active cardiac disease. A CT of the brain was performed and was normal. Laboratory testing was unrevealing. His symptoms resolved fully within several days following admission to the hospital. He was seen by a neurologist with a normal examination. An MRI of the brain was normal. An EEG was performed and was interpreted as abnormal, demonstrating "generalized spike-and-wave" (Fig. 30.1). He was discharged with a diagnosis of "seizure disorder," placed on carbamazepine (CBZ), and told not to drive a car. Following discharge he developed persistent nausea and stomach upset and stopped CBZ on his own 2–3 months later. He has otherwise been "fine" and presented for another opinion and desire to drive again.

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W.O. Tatum et al. (eds.), *Epilepsy Case Studies: Pearls for Patient Care*,
DOI 10.1007/978-3-319-01366-4_30,

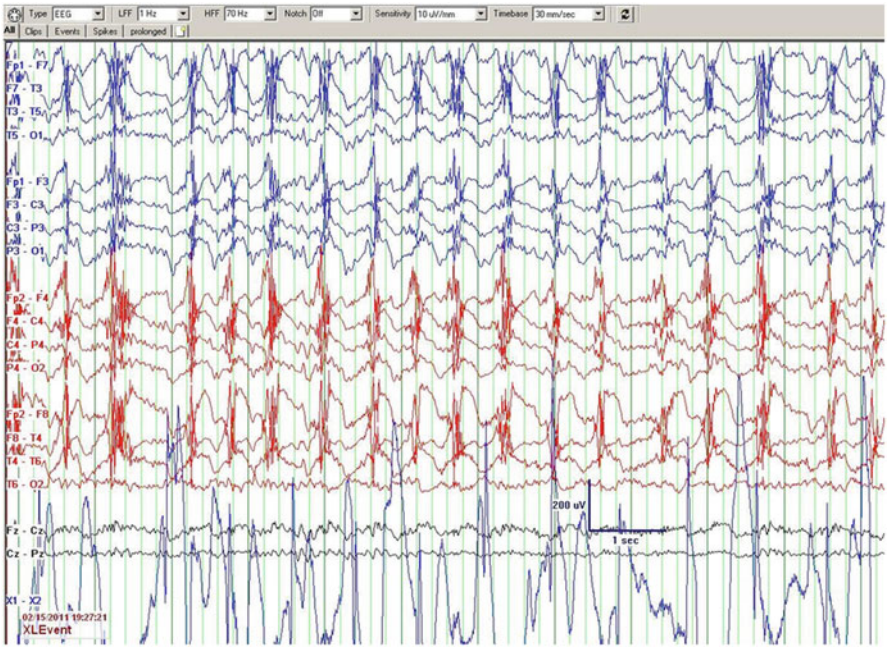

Fig. 30.1 EEG showing chewing artifact due to the alternating contraction and relaxation that produces phasic myogenic potentials that mimic polyspikes and spikes created by movement of the muscles of mastication

Clinical Questions

1. What does the clinical history suggest?
2. What does the EEG demonstrate?
3. What clinical seizure types would you expect for the EEG features suggested?
4. How common is a scenario like this?
5. What is the best course of action for this patient?

Diagnostic Discussion

1. The clinical history of awakening with spinning of the room associated with prolonged nausea and diaphoresis and preserved consciousness suggests vertigo. The prolonged duration, absence of impaired consciousness, lack of other seizure types, and history of epilepsy do NOT suggest focal seizures. The normal MRI and lack of additional cranial nerve or long track signs or symptoms did not implicate stroke. The acute presentation and lack of headache would not support migraine as the cause. Rather, the symptoms isolated to the vestibular system

suggest a peripheral localization to his complaints. The positional quality of the vertigo and previous head injury ultimately lead to a final diagnosis of benign paroxysmal positional vertigo.

2. The EEG demonstrates a common pattern of artifact that is created by bilateral muscle contraction to move the jaw (Fig. 30.1). Chewing produces this pattern of artifact. It is relatively easy to distinguish based upon the bitemporal location, the absence of a believable field, adjacent positive- and negative-phase reversals, polyphasic brief myogenic potentials, and the common occurrence, being present during routine EEG interpretation. These brief "spikes" and "polyspikes" due to artifact followed by an apparent "slow wave" due to DC currents produced during tongue movement and muscle relaxation mimic 1.5–2 Hz generalized spike-and-slow-waves. Video recording or behavioral notation by the EEG technologist would have been able to provide the behavioral correlation necessary to identify this common artifact.
3. The clinical correlation of a generalized spike-and-wave discharge noted on the EEG is nonspecific for seizure type. Still, generalized discharges suggest the correlation for generalized seizures. At a frequency of 3 Hz or faster, a genetic generalized epilepsy is suggested (or an inherited trait without seizures). Absence, generalized tonic-clonic, and myoclonic seizures would be anticipated. Polyspikes often correlate with myoclonic seizures. With the finding of <3 Hz generalized spike-waves (as in the present case), encephalopathic generalized epilepsy would be anticipated. A cognitive deficit would be expected in addition to other generalized seizure types (i.e., tonic or generalized tonic-clonic seizures). Since neither scenario is evident with this history, the importance of taking the EEG into the context of the underlying symptoms is self-evident.
4. The prevalence of misinterpreted clinical signs as epilepsy is reflected by the significant number of patients that are discovered following video-EEG monitoring. Overall, approximately 30 % of patients admitted for evaluation of "spells" do not have a correct diagnosis (of epilepsy). In these individuals >90 % are treated with antiseizure drugs. These treatments carry the risk of significant morbidity and even mortality (i.e., Stevens–Johnsons syndrome with CBZ). The prevalence of a misinterpreted EEG leading to the misdiagnosis of epilepsy is less clear, though it has been found to be significant in a several studies. The presence of artifact, benign variants, and normal variations have been contributors.
5. When a diagnosis is suggested that is different than the one implied by an existent treatment, consider the following. Trust your clinical acumen. Neurologists undergo 4 years of residency training to learn clinical neurology. By contrast, 0–3 months of clinical neurophysiology training is typically offered. Next, reevaluate the "tests" that do not "fit" with the clinical diagnosis—they could be wrong. Alternatively, consider a spurious value or independent finding that is irrelevant to the clinical diagnosis. In this case, if GSW were present it would have most likely occurred as an inherited trait independent of the clinical reason it was found. More likely was that the EEG was over-interpreted. Obtaining the outside record and reviewing the "abnormality" ultimately lead to a reversal of an epilepsy diagnosis. Even if the treating neurologist believed the EEG showed

GSW, CBZ would have been a poor AED selection due to the potential of CBZ to aggravate (an anticipated) generalized seizure disorder. Following his misdiagnosis the patient spent 2–3 months being "sick," had to work part-time, lost income, and was unable to drive for 8 months when he was on iatrogenic "disability."

Clinical Pearls

1. Epilepsy is a clinical diagnosis. Be suspicious when the "tests" and treatment do not "fit" the clinical diagnosis that is suspected.
2. Routine EEG is a qualitative test that is based upon experience and training and may be subject to errors of interpretation. Artifact, benign variants of uncertain significance, and normal variations do not confer a risk of epilepsy and may serve as pitfalls for less experienced interpreters.
3. Being biased or interpreting test results outside of the clinical context may be pitfalls for clinicians. In this case recovering the "abnormal" study was helpful in clarifying the underlying features because even if repeat EEGs are normal, it cannot "erase" prior "abnormal" recordings.
4. Incorrect treatments not only carry an immediate risk of morbidity (as in this patient) but may also carry a risk of mortality. What is less evident is the development of chronic disabling consequences. When other physiologic causes are misidentified even greater ramifications may be incurred (i.e., cardiac arrhythmia).

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Chapter 31
Surgery Candidate (Scalp EEG)

William O. Tatum IV

Case Presentation

A 47-year-old right-handed Indian-American female was self-referred for uncontrolled seizures. She was healthy only taking antiseizure drugs (ASDs) for "petit mal." She experienced a prolonged febrile convulsion at 2 years of age lasting 15 min with a fever of 103°. At that time she was told "nothing was wrong." She developed normally throughout childhood with above-average scholastic achievement. At 11 years of age she developed her first afebrile seizure. Seizures were diagnosed as "petit mal" seizures due to a prominent stare. As if in warning, she would develop an indescribable feeling just prior to a wide-eyed stare, subtle lip smacking, and impaired responsiveness for 45 s. Following this she would be sleepy with transient difficulty "getting the words out." Five ASDs failed to control her and she was maintained on lamotrigine and levetiracetam. Several seizures/month occurred with rare injury. She never experienced a "grand mal" seizure. Her neurological examination was normal. A brain MRI demonstrated left mesial temporal sclerosis (MTS) and EEG revealed left anterior temporal epileptiform discharges (Fig. 31.1). A surgical evaluation was recommended to her. Subsequently, a FDG-PET scan of the brain revealed hypometabolism of the left temporal lobe. Video-EEG monitoring revealed three focal seizures (Fig. 31.2). Neuropsychological testing revealed mild verbal memory deficit. A Wada test ultimately revealed 8/8 object recall and aphasia on left hemispheric injection, with 0/8 recall on right injection. A left amygdalohippocampectomy was recommended; however her son (an anesthesiologist) recommended against it. Ten years elapsed before surgery was performed. She has been seizure free for more than 2 years.

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W.O. Tatum et al. (eds.), *Epilepsy Case Studies: Pearls for Patient Care*,
DOI 10.1007/978-3-319-01366-4_31,

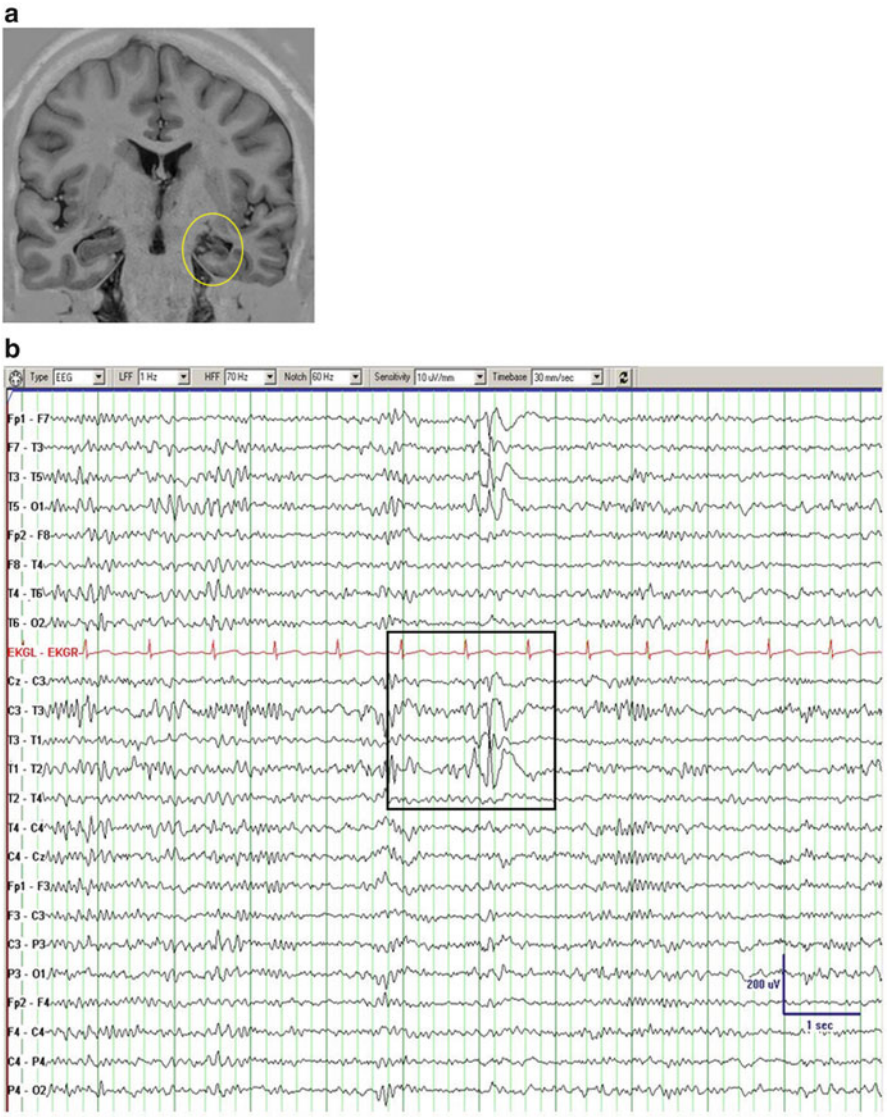

Fig. 31.1 (**a**) Brain MRI with left hippocampal formation atrophy (*yellow circle*) and (**b**) representative interictal EEG showing left temporal spikes (*box*)

Clinical Questions

1. What parts of the clinical history suggest focal seizures?
2. What is the likelihood that further ASDs will produce seizure freedom?
3. Why is seizure monitoring needed when the MRI is abnormal?
4. What further testing is required if surgery is to be pursued?
5. What is the prognosis after surgery for seizures and side effects?

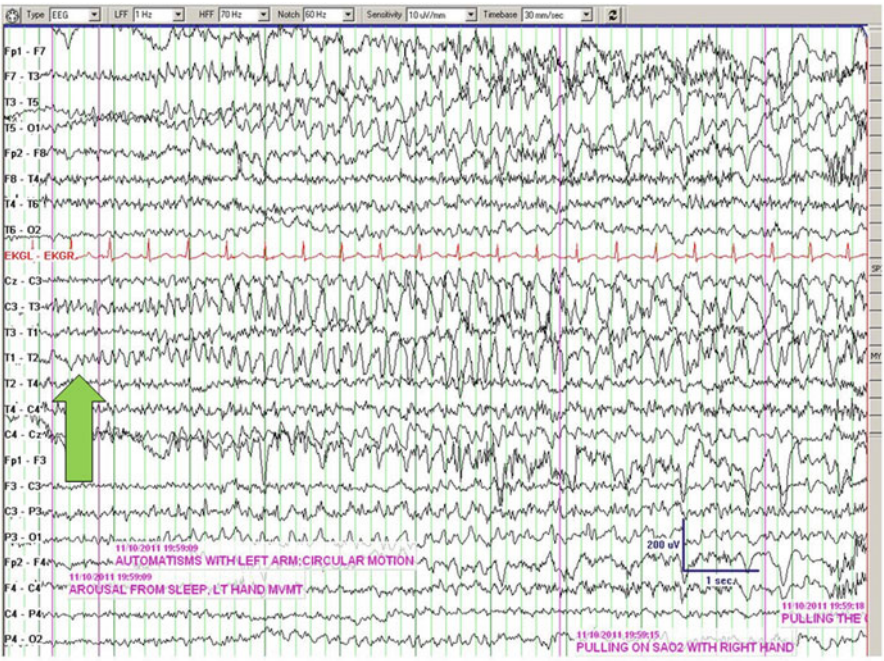

Fig. 31.2 Left rhythmic temporal theta onset during a focal seizure without awareness (*arrow*)

Diagnostic Discussion

1. The diagnosis of epilepsy is suggested by the paroxysmal recurrent episodes of impaired consciousness. Many patients describe their seizures as "petit mal" seizures when they are nonconvulsive, though in 70 % of adults, it is focal seizures, and not generalized seizures, that occur. In two-thirds of these individuals ASDs will not result in seizure control. Many adults with focal seizures experience a warning (aura), though it is the postictal state that distinguishes them from other events associated with transitory loss of consciousness, including absence seizures or "petit mal." If uncontrolled seizures are permitted to continue, there is a greater risk of higher accident and injury rates, psychiatric and cognitive deterioration (especially memory), social isolation, stigmatization, impaired self-esteem, and even mortality.
2. Approximately one-third of patients with focal seizures and 15–20 % with generalized epilepsy will remain refractory to ASDs. After the failure of two appropriate ASDs, given for an adequate duration at an effective dose, there is less than a 5–10 % likelihood that further AED changes will result in seizure freedom. It is important to exclude pseudoresistance as the reason for drug failure. An incorrect diagnosis may result in ongoing seizures because treatment of a non-epileptic seizure mimic is unlikely to respond to seizure medications.

Treatment with an incorrect AED (the wrong profile or too low a dose) will result in drug failure. The genetic generalized epilepsies, for example, may be aggravated by narrow-spectrum ASDs such as carbamazepine or phenytoin. Patient failure is yet another reason for poor results. When a noncompliance or an adverse lifestyle is encountered, the correct AED may be chosen but never given a reasonable chance of efficacy due to subtherapeutic use and drug or alcohol abuse.

3. When the MRI and interictal EEG are concordant, the likelihood of a correct localization is approximately 80 %. Ictal recordings are recommended to confirm the diagnosis of epilepsy. Approximately 30 % of patients admitted for epilepsy monitoring will not have epilepsy. The vast majority of these patients will have psychogenic non-epileptic seizures (PNES). Even in patients with epileptic seizures (ES), a significant minority may have both ES and PNES. Excluding incorrect AED choices can be achieved by classifying the seizures when they are captured. Recording seizures will also identify a solitary semiology and ictal EEG morphology to suggest unifocal epilepsy. Excluding more than one generator may be difficult based upon semiology. One example is the bitemporal epilepsy where staring episodes may be caused by focal seizures from each hemisphere independently.
4. The demonstration of a "lesion" (MTS in our patient) has the best predictive value as a localizing feature and as a favorable prognosticator. When all aspects of a "phase 1" evaluation are concordant (i.e., history and semiology, MRI, PET, video-EEG monitoring, neuropsychological testing), these candidates may "skip" and proceed directly to surgery without undergoing intracranial EEG monitoring for further seizure localization. In our patient, Wada testing was used to firmly localize language function and predict memory function after surgery. Functional MRI has been used to identify atypical areas subserving language, but has not yet been usable as a surrogate for memory function. The results are favorable and provide localizing information with impaired hippocampal function and a favorable outcome with respect to memory function.
5. This patient illustrates the most common surgically remediable syndrome of drug-resistant temporal lobe epilepsy (TLE). The presurgical evaluation above is classic for concordance in localization. Unfortunately, only a small percentage of potential surgical candidates are being referred to surgical epilepsy centers. Lengthy delays of 18–23 years are common. However, 50–70 % of patients become seizure free with limited morbidity postoperatively. Class 1 evidence exists proving that surgery is more effective than continued medical therapy. A favorable outcome from surgery exists when a lesion on neuroimaging is found to be responsible for focal seizures. Lesional epilepsy has a high rate of success, especially if it is due to hippocampal sclerosis as in our patient. Complications are related to the craniotomy, to the site, and to the extent of resected tissue. Nobody "wants" surgery, but it is important to present surgery as an option in a realistic and objective fashion. After declining for years our patient underwent surgery against the urging of her family. She had no complications and became seizure free as expected. She wished she would have undergone surgery sooner.

Clinical Pearls

1. Epilepsy surgery is a standard of care and should be considered early when a patient with focal seizures is proven to be drug resistant.
2. A lesion on neuroimaging is the best predictor of seizure onset and also for a seizure-free result.
3. Video-EEG monitoring should be performed before surgery. It will verify the diagnosis of epilepsy and exclude the possibility of other seizure mimics as the reason for drug resistance. In addition, it can provide localizing information about the site of seizure onset by demonstrating electrophysiological information that is concordant with the other "phase 1" evaluation.
4. TLE is the most common epilepsy surgery performed. TLE is often due to hippocampal sclerosis and the most common syndrome that is most amenable to surgery.
5. Though the ideal surgical candidate has the best predictability for a seizure-free outcome, epilepsy surgery is more likely to result in seizure freedom when patients have failed >2 appropriate AED trials.

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Chapter 32
Surgery Candidate (Intracranial EEG)

William O. Tatum IV

Case Presentation

A 54-year-old right-handed female was in good health until she was 28 years old. Without risk factors, she developed recurrent focal seizures with impaired consciousness that intermittently evolved to convulsions. After the seizures failed to be controlled after trials of five ASDs, she was self-referred and subsequently underwent a presurgical evaluation for drug-resistant seizures. A high-resolution 3-T brain MRI using an epilepsy protocol was normal. FDG-PET demonstrated left temporal hypometabolism. She was admitted for video-EEG monitoring to further characterize her seizures. Scalp interictal EEG revealed left > right bitemporal epileptiform discharges with phase reversals at the T1/F7 and T2/F8 derivations (75:25 ratio). Three focal seizures (1–3) and one focal seizure that evolved to a convulsion (4) were captured. Independent left ($n = 2$; seizure 1 and 4) and right ($n = 2$; seizure 2 and 3) temporal onsets were captured. The semiology demonstrated a sudden blank stare without warning, with impaired consciousness, and manual automatisms for 40 s following which she was agitated and "could not talk" (left temporal onset on scalp EEG [scEEG]). In addition, a second semiology (infrequent by report) manifested as a blank stare, impaired consciousness, and left arm posturing, and afterwards she had similar trouble expressing herself. Wada testing demonstrated left hemisphere dominance for language and bilateral memory function. She was highly motivated toward surgery, so she was implanted with bilateral subdural strips and depth electrodes (Fig. 32.1). All seizures ($n = 8$)

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W.O. Tatum et al. (eds.), *Epilepsy Case Studies: Pearls for Patient Care*,
DOI 10.1007/978-3-319-01366-4_32,

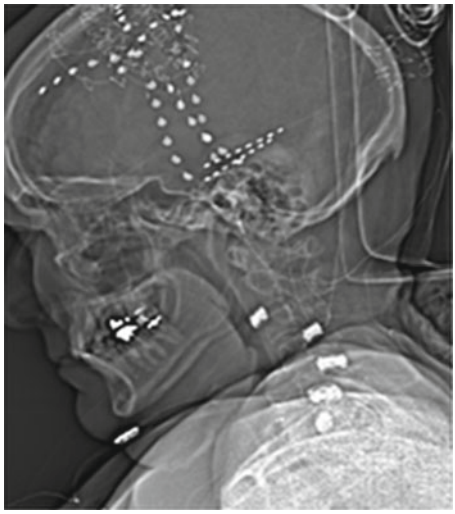

Fig. 32.1 Lateral skull X-ray of implanted electrodes using bilateral strip electrodes to survey temporal and extratemporal cortex and depth electrodes (*arrows*) to sample mesial temporal lobes

demonstrated left temporal onset (Fig. 32.2) with a "switch" to the right strips/depths (b) noted in her two seizures associated with left-sided dystonic posturing. She underwent a left temporal lobectomy and has been a class 2 outcome.

Clinical Questions

1. In the evaluation for epilepsy surgery, what factors are considered?
2. What aspects of the presurgical evaluation are predictive of outcome?
3. When are intracranial electrodes used?
4. What types of electrodes and location are implanted?
5. What is the likelihood of a seizure-free outcome following intracranial EEG (iEEG)?

Diagnostic Discussion

1. The first step in evaluating patients for epilepsy surgery is a careful history and examination. In the history, identify potential causes for epilepsy by addressing risk factors for seizures (i.e., febrile seizures, head injury, encephalitis, abnormal brain MRI, and developmental anomalies). Neuroimaging techniques (high-resolution brain MRI and PET) will identify the presence of an anatomic and functional lesion. Video-EEG monitoring lateralizes and localizes the electrophysiology of the interictal and ictal electroclinical component to complete the initial surface-based evaluation (phase 1) of the localization of the epileptogenic zone.

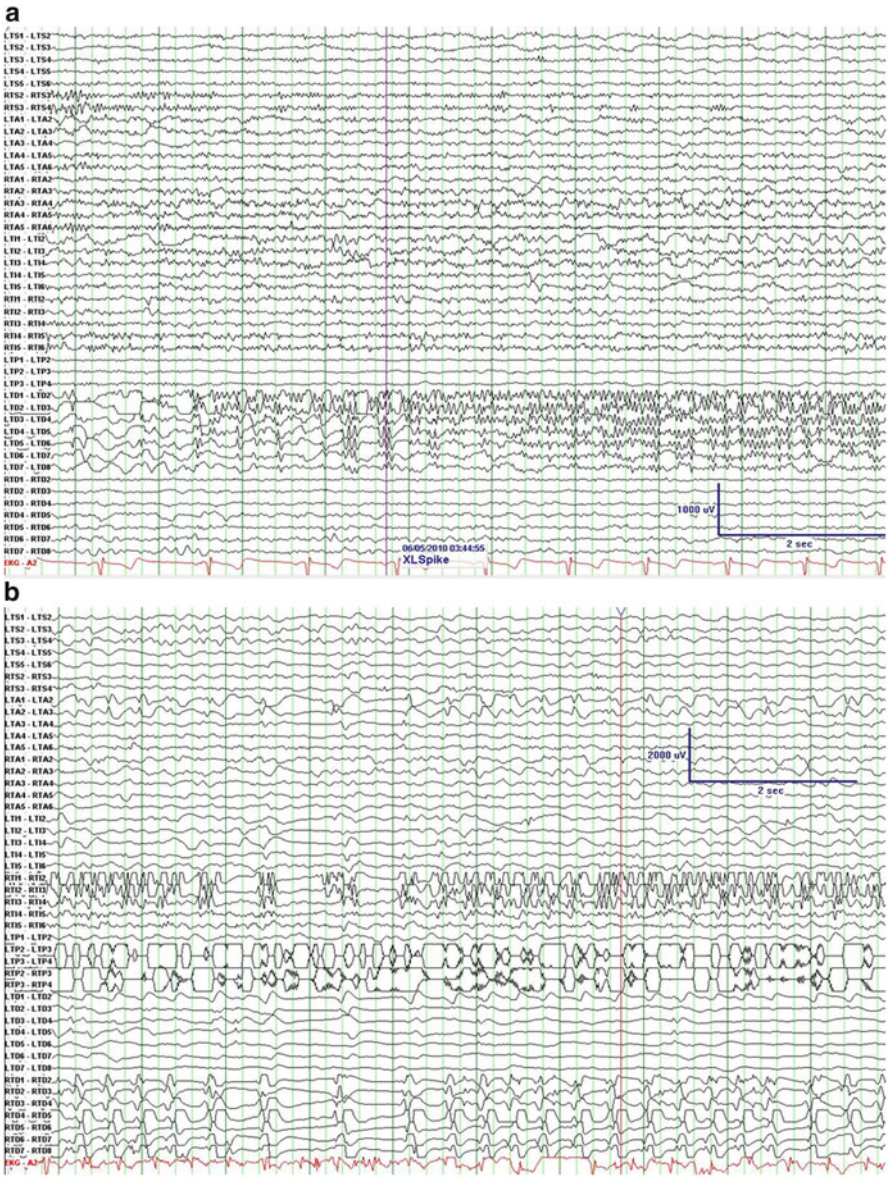

Fig. 32.2 (**a**) Representative iEEG with left regional ictal fast activity in the depth at seizure onset. (**b**) Periodic complexes in the right depth and fast activity in the strips at termination. *L/RST* left/right superior temporal, *L/RTA* left/right temporal anterior, *L/RTI* left/right temporal inferior, *L/RTP* left/right temporal parietal, *L/RTD* left/right temporal depths. Sensitivity 50 μv/mm. Settings of 1–70 Hz

2. The brain MRI is the most predictive aspect of the presurgical evaluation in localizing the epileptogenic zone. Recent advances have improved both the technique and resolution allowing it to better define neuroanatomy of hippocampal sclerosis, cavernous vascular malformations, focal cortical dysplasias, malformations of cortical development, and tumors (i.e., low-grade gliomas). When concordance with other techniques is noted, success from surgery is excellent. However, scEEG has limitations and may not be well defined. In our patient, there were discordant results in the initial evaluation. The success of epilepsy surgery lies in localizing one epileptogenic zone that can be safely resected. Patients must be drug resistant and motivated to undergo an evaluative surgical procedure.
3. iEEG is necessary when discordant information (i.e., bitemporal seizures) is evident on scEEG. It is also useful when eloquent cortex is or may be involved and when poor definition of the epileptogenic zone remains after initial surface-based evaluation. The attempt to localize patients with iEEG is based upon the results of the noninvasive evaluation. Scalp interictal and ictal EEG coupled with the semiology form the basis of localization, though the sensitivity is limited to discern the onset from propagated patterns, especially if the generators are deep-seated or cortically based. Invasive EEG is frequently used when insufficient localizing information is present from the noninvasive evaluation. Depth and subdural strip or grid electrodes are often combined (figure) to record smaller pools of neurons that are unable to generate a signal adequate for scalp detection.
4. iEEG has improved sensitivity compared with scEEG. Common neocortical based low-voltage fast activity composed of beta and gamma frequencies is the most attenuated and may not be detectable by scEEG to identify seizure onset. Invasive electrodes have greater sensitivity, but more restricted sampling, to detect seizures earlier. They provide a "coned-down" view, though they imply a greater degree of complexity and potentially more limited expectation of becoming seizure free after surgery. Depth electrodes and subdural strip (and grid) electrodes are the two most commonly employed iEEG electrodes. Depth electrodes are multi-contact probes that are inserted into the brain. Small regions of brain are assessed but deep structures may be evaluated. The risk of bleeding is small (<5 %) and is surgeon dependent. Subdural electrodes imbedded in polyurethane strips (and grids) are placed via burr holes (and craniotomies). Grid placement carries the highest risk of bleeding, but may be used for functional brain mapping using electrical cortical stimulation.
5. Seizures commonly propagate to other brain regions and may falsely lateralize scalp ictal EEG as in our patient. Propagated frequencies are often slower than ictal onset frequencies, facilitating false scEEG lateralization combined with a propagated semiology, as in our patient. Electrographic patterns at seizure termination are poorly predictive of surgical outcome. The outcome after intracranial electrode use (phase 2) is less favorable than lesional surgery. Presurgical evaluation strategies for patients that undergo iEEG for focal seizures remain highly variable both for electrode type and for their placement (electrode array). Advancements in neuronavigational systems guide electrode placement and

likely have contributed to reduced complication rates. The success of iEEG is governed by its application. Centers that always use iEEG will have better outcomes than those that only use it for the "worst" cases. Skilled epilepsy surgeons will have better outcomes and reduced complications than those that infrequently perform operations. Our patient was counseled on our lowered expectation of a seizure-free outcome. She underwent a left temporal lobectomy and had "success" in seizure reduction (>90 %). She perceived this as improvement, allowing her a greater degree of freedom and independence.

Clinical Pearls

1. The success of epilepsy surgery lies in localizing one epileptogenic zone that can be safely resected. Noninvasive evaluations (phase 1) are performed prior to invasive evaluations (phase 2) when poor localizing information, discordant information, or involvement of eloquent cortex (i.e., language or motor function) may be involved.
2. Semiology (and scEEG) may be falsely lateralized, as in this case, suggesting bitemporal epilepsy. iEEG has improved sensitivity compared with scEEG. When the ictal onset is composed of beta and gamma frequencies that are normally attenuated, seizures may not be detectable by scEEG at the onset.
3. The physician should ensure that the patient has realistic expectations before iEEG, explaining the possibility of no surgery, incompletely effective surgery (<class 1 outcomes of seizure freedom), and potential complications from a surgical procedure.
4. The prognosis for a seizure-free outcome when iEEG is used is, in general, less favorable than surgery that is based upon resection of a lesion or one that involves concordant information in the noninvasive evaluation.

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Chapter 33
Drug-Resistant Surgical Failure

Ricky W. Lee and Gregory D. Cascino

Case Presentation

A 45-year-old right-handed Caucasian male was referred for evaluation of drug-resistant localization-related epilepsy. His seizures were characterized by an abrupt onset of staring with behavioral arrest, lip smacking, and transient impairment of consciousness. Occasionally, his focal seizures evolved into generalized seizures. His epilepsy had been refractory to multiple antiepileptic medications, so he underwent a comprehensive evaluation including an MRI of the brain which was normal. Prolonged video-EEG monitoring recorded seizures of left frontotemporal onset. He subsequently underwent surgical placement of intracranial electrodes for intracranial EEG (iEEG) monitoring. He was implanted with an electrode array providing left frontotemporal coverage for definitive lobar localization and to provide language mapping using electrical cortical stimulation, if necessary. Re-monitoring with iEEG demonstrated left temporal lobe onset for his typical seizures. He underwent *en bloc* left temporal lobectomy. He was seizure free for 2 months after his resective surgery, though unfortunately his seizures returned and again he manifested drug-resistance. Subsequently, he returned for reevaluation. Brain MRI (Fig. 33.1) showed only anticipated postoperative changes. Postoperative scalp video-EEG monitoring again recorded seizures of left temporal onset (Fig. 33.2).

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W.O. Tatum et al. (eds.), *Epilepsy Case Studies: Pearls for Patient Care*,
DOI 10.1007/978-3-319-01366-4_33,

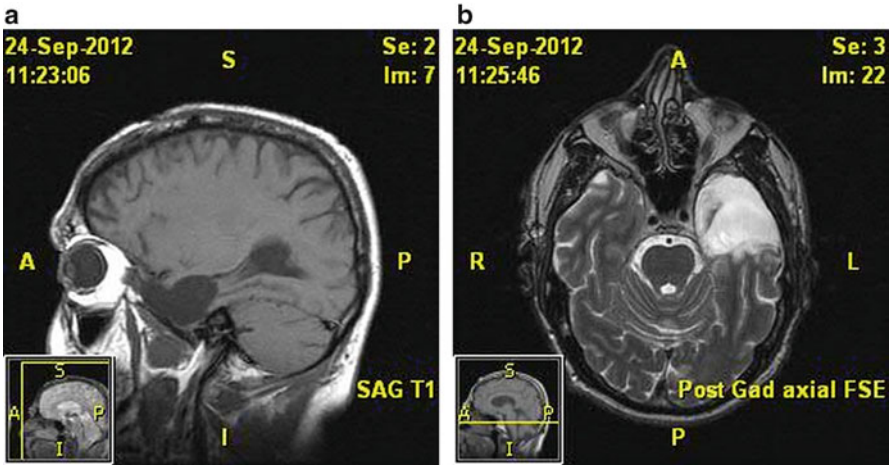

Fig. 33.1 (**a**, **b**) Brain MRI demonstrating expected postoperative changes after en bloc left anterior temporal lobectomy

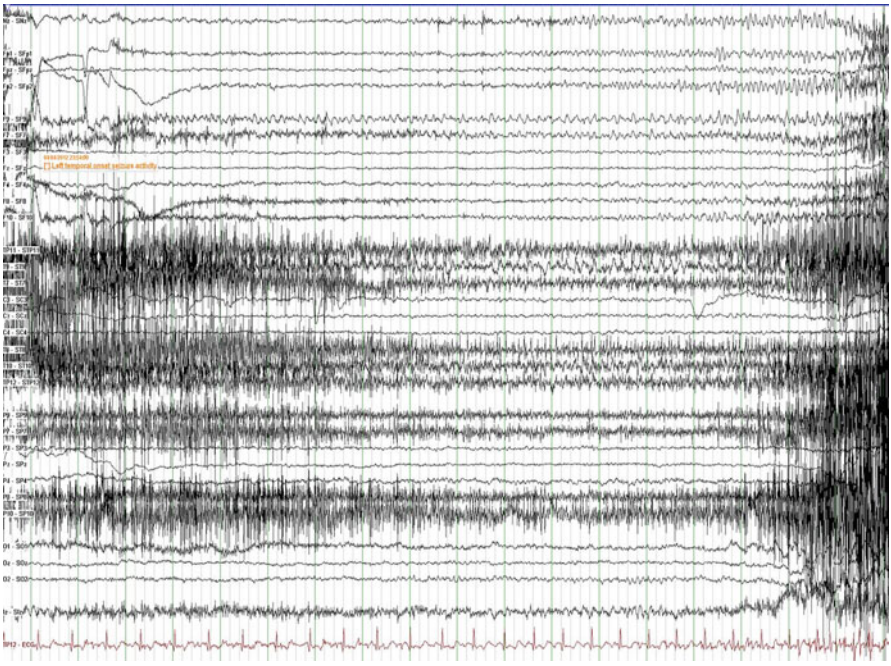

Fig. 33.2 EEG showing a left temporal lobe seizure

Clinical Questions

1. What are the possible explanations for failed epilepsy surgery?
2. What is the expected outcome for resective surgery in patients with a non-lesional preoperative brain MRI?
3. When should iEEG be considered?
4. Is reoperation in this patient an option?
5. What options are available if reoperation is not possible?

Diagnostic Discussion

1. Unfortunately, despite a comprehensive presurgical evaluation, 30–40 % of patients undergoing surgical treatment continue to have disabling seizures after surgery. Studies have shown that recurrence of seizures most often occurs within the first year of surgery. The reasons that lead to failed epilepsy surgery can be roughly divided into three groups. Group 1 comprises patients with incorrect localization of the epileptogenic zone (i.e., temporal resection for "pseudotemporal" lobe epilepsy). Group 2 is associated with correct localization but inadequate excision of the epileptogenic zone. This is especially true in cases of insufficient hippocampal resection in mesial temporal lobe epilepsy or when the epileptic zone cannot be removed because it involves eloquent (functional) cortex. Group 3 is due to a second generator that existed preoperatively (i.e., dual pathology) or that developed after the initial resection.
2. After resective epilepsy surgery, rarely would MRI be able to identify potentially epileptogenic lesion. In the absence of a potentially epileptogenic lesion on MRI, localization of the site for epilepsy surgery is more complex and postoperative outcome is generally less favorable than that in lesional epilepsy surgery. Patients who underwent anterior temporal lobectomy have been shown to have an excellent outcome in 62 % of those with no MRI lesion versus 85 % of those with MRI lesion. The outcome in patients with non-lesional frontal lobe surgery is even less favorable. One study showed that of patients who underwent frontal lobe surgery, only 40 % of those without MRI lesion had an excellent outcome versus 72 % of those with an MRI lesion.
3. iEEG monitoring is considered to be the gold standard for seizure localization. However, due to inherent morbidity and mortality, the use of iEEG has to be judiciously determined. iEEG is especially important for patients with non-lesional MRI in which an epileptogenic focus is poorly defined. Often, functional imaging studies (i.e., single-photon emission computed tomography [SPECT] and positron emission tomography [PET]) are used to guide the implantation of intracranial electrodes. In the absence of an MRI lesion, intracranial electrode implantation tends to be more extensive. It is not unusual that additional electrodes need to be implanted if initial implantation yields

inadequate seizure localization. Unfortunately, studies have shown an increase in complication rates related to longer iEEG monitoring and a greater number of electrodes.

4. Unsuccessful epilepsy surgery can lead to significant frustration on the part of patients, their families, and their health care providers. Sometimes, a repeat surgical evaluation leads to consideration of another epilepsy operation. Approximately 20–50 % of patients are seizure free after reoperation. Repeat surgery carries not only reduced likelihood of seizure freedom but also higher risk of morbidity. Several studies have demonstrated a transient or a permanent complication rate of 20–25 % associated with reoperation, which is not insignificant. Prognostic factors that have been associated with a favorable seizure outcome include (1) completion of a previous partial lesionectomy and (2) extending the previous resection when the prior localization has been validated.
5. Many patients with medically and surgically refractory epilepsy are not suitable for repeat surgery. Electronic neurostimulators and a low-glycemic diet are potential alternatives. Unfortunately, rarely do these therapeutic interventions render patients seizure free. Vagus nerve stimulation (VNS) is an FDA-approved adjunctive therapy for localization-related epilepsy, though it may be effective for other forms as well. It is generally well tolerated. The most common side effects include hoarseness, coughing, or problem swallowing. Studies have shown 50 % of seizure-reduction in 30–40 % of patients. Deep brain stimulation (DBS) and a responsive neurostimulator (RNS) involve the implantation of a device that sends electrical impulses to specific parts of the brain to provide therapeutic benefits. In the USA, DBS is only approved to treat movement disorders and, like the RNS, is still an experimental procedure in patients with epilepsy. The ketogenic diet is a high-fat, adequate-protein, and low-carbohydrate diet to treat uncontrolled epilepsy and is especially useful in the pediatric population. Due to its stringent requirements, the ketogenic diet is not well tolerated by many patients. Instead, a modified Atkins diet or low-glycemic diet can be considered. Investigational ASDs may also offer hope to a few patients who have found little success with other treatments.

Clinical Pearls

1. Caring for patients with drug-resistant epilepsy that have failed epilepsy surgery is challenging and requires a multidisciplinary approach.
2. Reoperation may be an option in selected patients failing resective epilepsy surgery, especially when an initial incomplete resection of a lesion or of the seizure onset zone is present. Reoperation carries a lower likelihood of success and may entail a greater risk of complications.
3. Electronic neurostimulators and high-fat/low-glycemic diets can be helpful when reoperation is not possible. However, rarely do these alternative therapies result in a seizure-free outcome.

4. Alternative non-AED treatments are usually well tolerated and lack the same side effect profile commonly associated with medications. In addition, they may also reduce the total seizure burden. Therefore, they should be considered when drugs are ineffective and reoperation is not able to provide a favorable result.

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Chapter 34
Epilepsy and Disability

Joseph I. Sirven

Case Presentation

A 34-year-old man presents with the chief complaint of recurrent "spells." The episodes began approximately 2 years ago after he had been involved in an automobile accident and suffered a closed head injury. The spells were characterized by a sensation of "zoning out" that was preceded by a fearful sense of panic. They occurred at least twice a week and lasted between 50 and 90 s. After the event, he felt tired and had difficulty focusing on his work or during his daily activities. He worked as a District Attorney and had court duties and appearances that were required on a nearly daily basis.

No past family history of similar events was present. He noticed that after his spells he was able to return to his work, but he always felt that his cognition and especially his word-finding ability were compromised. He presented for a definitive diagnosis and also counseling regarding what to tell his employer. Imaging studies of his brain were normal. A routine scalp EEG was performed and demonstrated in Fig. 34.1.

Clinical Questions

1. What does the EEG show?
2. What are the implications for the individual's work?
3. Can his employer fire him because of these spells?
4. Is epilepsy covered by federal law to prevent discrimination?
5. Will this individual be eligible for Social Security Disability?

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W.O. Tatum et al. (eds.), *Epilepsy Case Studies: Pearls for Patient Care*,
DOI 10.1007/978-3-319-01366-4_34,

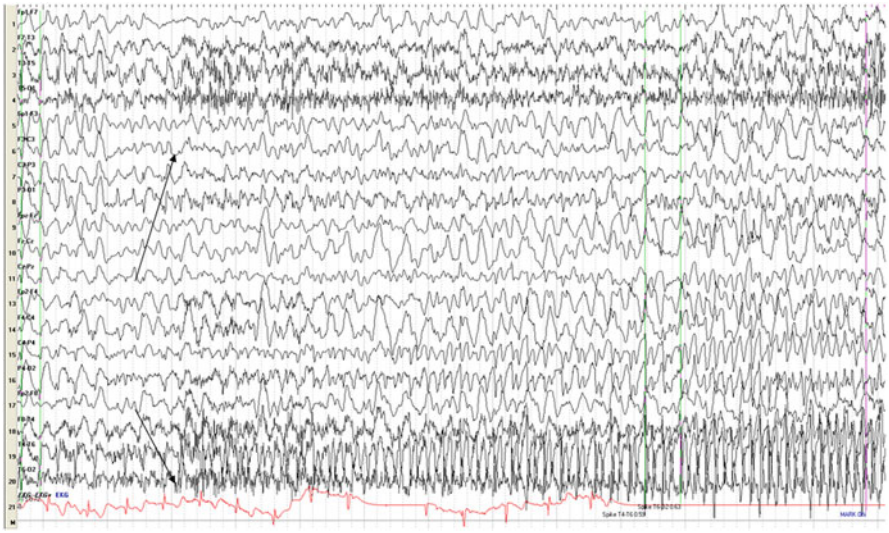

Fig. 34.1 EEG demonstrating an electrographic seizure involving the right hemisphere. Note the presence of superimposed temporal-occipital myogenic artifact (*arrows*)

Diagnostic Discussion

1. The EEG demonstrates an electroclinical seizure that involves the right hemisphere, though it is only associated with a subjective sensation of panic. With the patient history of recurrent episodes and an ictal EEG, the recording is therefore diagnostic of localization-related epilepsy. Antiepileptic medication should be recommended and be the first line of therapy.
2. Unprovoked focal seizures are often associated with cognitive dysfunction as a comorbidity. Short-term memory and language difficulty are not uncommon when the temporal lobe is involved. However, the symptoms produced by recurrent seizures depend upon the anatomic localization of seizure-onset zone. Therefore, if the seizures were not controlled, there could be significant implications for a patient's career. Given that this patient is a professional who is employed as an attorney, the utilization of his language and memory skills are crucial to the proper execution of work-related duties. If his seizures are controlled without side effects, he should be able to continue gainful employment.
3. According to the Americans with Disabilities Act (ADA) passed in 1990, the US law ensures equality of opportunity, full participation, independent living, and economic self-sufficiency for individuals with disabilities. Civil rights are addressed across several domains and include employment discrimination. Discrimination includes both public services and those involving public accom-

modations. Title I of the ADA specifically protects people with disabilities from being discriminated against in the workplace. Any discrimination involved in hiring, advancement or discharge of employees, compensation involving job training and job execution, and equal conditions and privileges of employment are subject to the ADA. Titles II and III prohibit discrimination based on disability by public entity. This includes limiting access to public transportation at both the local and state level and requires public accommodations be available if needed. An individual cannot legally be fired because of seizures or a diagnosis of epilepsy.

4. In 2008 the ADA provided protection for patients with disabilities that included epilepsy by adopting an amendment to the ADA. This amendment specifically addressed epilepsy. Even though seizures are episodic in nature, their occurrence (despite remission) could disable one's lifestyle. Therefore, our patient has protection by the US law. In addition, reasonable accommodations should be made to prevent undue hardship. These include carpeting to cushion falls, a private area to rest after a seizure, day-shift working hours, waiving nonessential tasks, or reassignment to an alternate job (i.e., a non-driving position). Additionally, eligible employees may utilize the Family and Medical Leave Act to take up to 12 weeks of unpaid leave within a 12-month time period.
5. With regard to qualifying for Social Security Disability, the Social Security Administration does consider epilepsy a condition that may lead to disability. There are two inclusions for epilepsy. One involves epilepsy that is convulsive and the other exists for those with nonconvulsive seizures. In order to qualify for benefits with convulsive epilepsy, at least one seizure a month must be present with at least 3 months of antiepileptic drug treatment. The seizures must be either daytime seizures with convulsions that involve a loss of consciousness or nighttime seizures with symptoms that result in impairment of daytime activities. To qualify under nonconvulsive epilepsy, one must prove that there is at least one seizure per week in spite of at least 3 months of compliance with a prescription antiepileptic medication. In addition, the seizures must significantly interfere with daily activities or create abnormal postictal behavior. Lastly, if one does not meet the criteria spelled out above, one can qualify for disabilities under the medical vocational guidelines. This means that the symptoms of epilepsy must interfere with daily activities such that there are no jobs available that one could consistently perform. However, this involves a more rigorous review prior to receiving disability. The claims examiner will address the individual's age, level of education, transferable work skills, and other medical and psychiatric conditions. He will take into account the individual's ability to work as well as any restrictions that the treating physician has placed on the (e.g., driving restrictions and avoidance of work around machinery). In general, one must show that you are unable to perform any work-related activities on a full-time basis. Simply voicing that you are unable to do your job is insufficient. Older individuals and

those that have less education and fewer transferable employment skill sets have an increased chance of being awarded disability benefits.

Clinical Pearls

1. Epilepsy is protected by the Americans with Disabilities Act and the 2008 ADA amendment.
2. One can qualify for Social Security Disability.
3. Seizures are not required to be the only issue impairing the ability to work. Cognitive issues such as those associated with treatment may also be associated with employment disability.
4. One should refer patients to an advocacy organization, such as the Epilepsy Foundation of America, when discrimination or disability occurs.

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Chapter 35
Memory Loss and Seizures

John Lucas

Case Presentation

A 22-year-old male underwent a left anterior temporal lobectomy for drug-resistant epilepsy. He presented with complaints of memory and word-finding difficulties. He was first diagnosed with epilepsy at age 21 when he experienced a generalized tonic–clonic seizure. Risk factors for epilepsy included a motor vehicle accident with closed head injury at age 16 and repeated self-asphyxiation "play" during early adolescence. Prior to diagnosis, he reported a 9-month history of brief, recurrent, stereotyped spells characterized by sudden-onset "head rush" followed by a sense of "excitement" in his chest and extreme diaphoresis initially misdiagnosed as anxiety. He was unresponsive during his spells and afterwards felt "drained," with incomplete memory of the event. He became resistant to ASDs and underwent epilepsy surgery. A preoperative MRI, PET, and neuropsychological testing prior to surgery were normal. Video-EEG monitoring had interictal epileptiform discharges and three typical seizures with ictal onset in the left temporal region corroborated and localized by invasive monitoring with depth electrodes. Wada testing revealed left hemisphere dominance for language and bilateral representation of memory functioning. The patient underwent left anterior temporal neocorticectomy and partial left amygdalohippocampectomy guided by language mapping. Surgery resulted in seizure-free outcome and he returned to college 6 months later to complete an Associate's degree that he had started prior to the onset of his generalized seizures. At that time he noticed new-onset cognitive difficulties. He reported that it was taking him longer to learn new information in class and, even after understanding the material, he was less able to process and fully explain it to others or demonstrate his

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DOI 10.1007/978-3-319-01366-4_35,

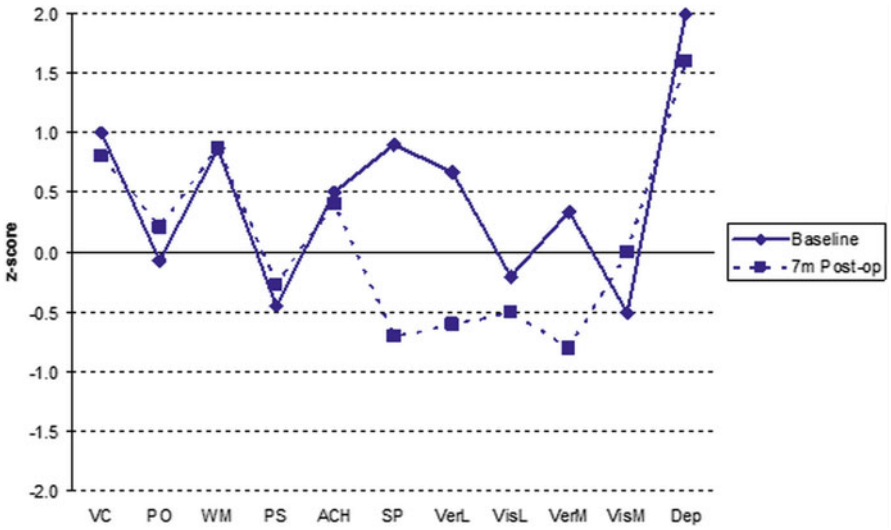

Fig. 35.1 Plot of composite *z*-scores across representative cognitive domains assessed 1 month prior to surgery (*baseline*) and 7 months post surgery. *VC* verbal comprehension, *PO* perceptual organization, *WM* working memory, *PS* processing speed, *SP* semantic processing, *VerL* verbal learning, *VisL* visual learning, *VerM* verbal memory, *VisMem* visual memory, *Dep* depression screen. *Shaded area* reflects the range of "normal" limits

knowledge on tests. He was referred for repeat neuropsychological studies (Fig. 35.1) to evaluate his cognitive change and to offer recommendations to improve functional status.

Clinical Questions

1. Does the patient demonstrate any postoperative cognitive impairment to substantiate his subjective complaints?
2. Has there been any change in cognitive function compared with his presurgical status?
3. Does the neuropsychological profile reflect change associated with the neuroanatomical resection?
4. Are there any factors other than surgical resection that could also contribute to cognitive change?
5. What therapies or resources could be recommended to improve cognitive functioning in this patient?

Diagnostic Discussion

1. Cognitive test performances that fall within 1 standard deviation above or below the normative mean ($z=0$) are typically considered to be within normal limits (shaded area of figure). Examination of this patient's postoperative test results alone reveals that he performed within the normal range across all cognitive domains assessed.
2. With the benefit of comparing his presurgical data, it can be seen that even though postoperative results are technically within normal limits, verbal learning, verbal memory, and semantic processing abilities (i.e., object naming and semantic verbal fluency) have declined. The longitudinal data support the patient's subjective experience of acquired difficulty learning and expressing knowledge in his college courses.
3. The neuropsychological findings reflect a strong clinical correlation with what is anticipated to occur with surgery involving the left temporal lobe in patients with a normal preoperative brain MRI. Wada testing revealed left hemisphere language dominance and intact left hemisphere memory functioning in this patient. The language-dominant anterior temporal lobe is believed to play an important role in semantic processing, linking together areas of the brain containing semantic information. Together with hippocampus and other medial temporal lobe structures, these systems within the language-dominant hemisphere are also essential to new learning and memory of verbal information.
4. Surgical resection is not the only risk factor for cognitive impairment on postoperative testing in epilepsy patients. Preexisting neurodevelopmental conditions such as learning disability, attention-deficit disorder, or low intellectual function can cause or enhance functional cognitive deficits, but can often be predicted by preoperative testing or ruled out, as was the case with this patient. Uncontrolled seizures can cause progressive memory decline in individuals with temporal lobe epilepsy due to interruption in the neuronal mechanisms underlying memory encoding (i.e., hippocampal long-term potentiation). In this patient, however, seizures were controlled by surgery and cannot account for the observed memory decline. Use of ASDs, sleep disturbance, and mood disorders can impair memory, often through deficits in attention. This patient is on fewer ASDs at lower doses following his surgery, and he reported no sleep difficulty. He reported depressed mood at the time of postoperative evaluation; however, mood testing at baseline revealed more severe depression prior to his surgery. After excluding potential contributing factors, it appeared that the observed cognitive changes could not be accounted for by nonsurgical factors.
5. Enough time had passed for the effect from acute surgical "trauma" to resolve. Therefore, formal cognitive rehabilitation and development of compensatory language and learning strategies were recommended, and a referral for outpatient cognitive rehabilitation was made. He could also benefit from more immediate and direct assistance with his college studies. Although his overall neuropsychological profile falls within normal limits, tasks that were once effortless when his

semantic processing/verbal learning were above average are more difficult and require more effort now that these abilities are below average. The Student Services Center at his learning institution was approached to offer a study skills evaluation to help him develop more effective and efficient ways to learn new information. Other services, such as tutoring or note-taking assistance may also facilitate his ability to learn. His cognitive profile suggested that he was likely to experience difficulty and frustration on tests employing open-ended or essay questions. Hence, allowing him to take multiple-choice tests where semantic retrieval demands are minimized was suggested. If he had continued having difficulty pursuing career goals, despite appropriate academic accommodations, vocational counseling could help identify alternate career paths that fit better with his retained cognitive strengths. Finally, providing psychological intervention for his residual depression at this stage may prevent progressive worsening of mood and disability going forward.

Clinical Pearls

1. A single neuropsychological study at one point in time may identify areas of cognitive weakness or impairment as compared to normative standards but may not always be able to determine whether a patient has *declined* from a previously higher level of functioning.
2. Obtaining baseline neuropsychological studies prior to epilepsy surgery can facilitate identification of specific areas of cognitive decline post operation. This is especially relevant when the surgical target will involve functional tissue that could affect cognition.
3. The temporal lobes are the most common location for seizure onset. The medial temporal lobe (i.e., hippocampus) has the lowest threshold for seizure activity in the brain and is also critical for new memory formation. The anterior temporal lobe of the dominant hemisphere is especially important for semantic processing, particularly naming ability. Removing functional tissue from the left temporal lobe may result in a decline in naming, new learning, and memory that is quantifiable on neuropsychological testing.
4. There are many variables, other than surgical resection, that may contribute to memory deficits in patients with epilepsy. These include seizure variables (e.g., frequency, location of seizure focus, location of resection, AED use), mood disorders, sleep disorders, or preexisting neurodevelopmental disorders such as learning disability, attention-deficit disorder, or low intellectual functioning. Comprehensive pre- and postoperative neuropsychological assessment can help guide recovery and rehabilitation plans, contributing to improved outcomes in the functional status of surgical epilepsy patients.

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Chapter 36
Status Epilepticus Convulsive

Joseph I. Sirven

Case Presentation

A 23-year-old male with a history of localization-related epilepsy was taking Carbamazepine, 400 mg PO BID. His epilepsy would manifest as recurrent focal seizures that intermittently progressed to convulsions. He was seizure-free as long as he remained compliant with his AED. He was reported to have recently been away on a camping trip with several of his friends. While he was away, he was sleep-deprived due to staying up until late hours of the early morning. Shortly after midnight he developed a "grand mal" seizure. This repeated two more times and his friends called 911 for help. He was transported to the nearest hospital and had persistent impairment of his consciousness. In the Emergency Department (ED), he did not answer questions and was "just staring at the nurses". A brain CT was unrevealing. Laboratory evaluation did not demonstrate any abnormalities in his electrolytes or complete blood count with differential. A toxicology screen was negative for illicit substances and alcohol. A carbamazepine level was non-detectable.

An EEG was obtained in the ED (Fig. 36.1).

Clinical Questions

1. How does the EEG help in making the diagnosis?
2. What is the definition of status epilepticus?
3. What should comprise the initial evaluation of status?

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W.O. Tatum et al. (eds.), *Epilepsy Case Studies: Pearls for Patient Care*,
DOI 10.1007/978-3-319-01366-4_36,

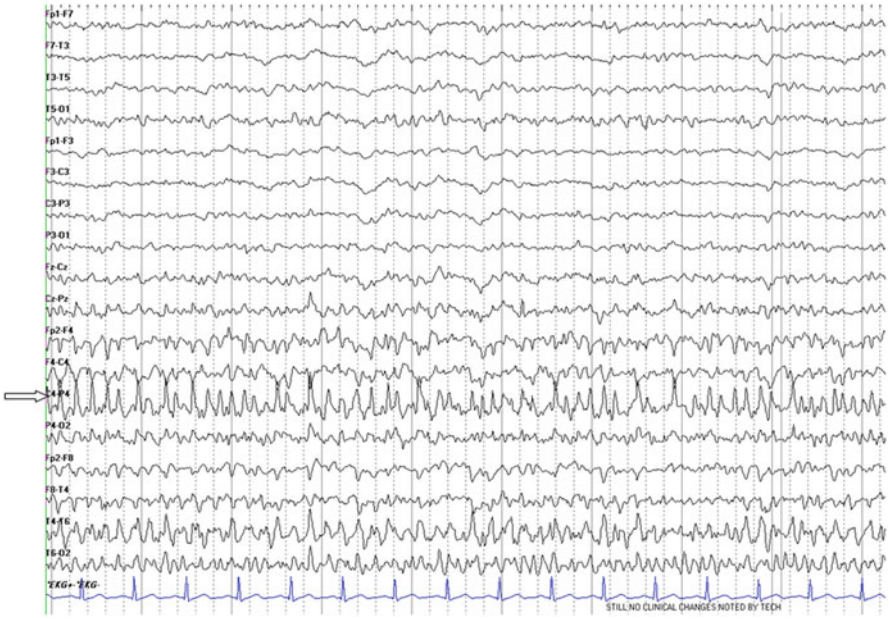

Fig. 36.1 Focal electrographic status epilepticus confined to the right hemisphere

4. What is the initial approach to treatment?
5. What role does the EEG have in the management of this condition?

Diagnostic Discussion

1. This EEG shows ongoing status epilepticus with ongoing seizure activity emanating from the right hemisphere (see arrow on Fig. 36.1). This patient initially had convulsive status epilepticus that evolved to non-convulsive seizures to explain the impaired consciousness in the ED.
2. Status epilepticus has been defined as 30 min or more of a prolonged seizure or the patient does not return to their baseline state between recurrent seizures. Operational definitions now include any seizure that is greater than 5 min. Status epilepticus is a medical emergency and newer definitions reflect the move toward earlier treatment.
3. Status epilepticus is a serious life-threatening condition with a risk of significant morbidity and mortality. The initial evaluation includes neuroimaging studies of the brain to identify a potential structural basis of status and the need for treatment of the cause. Laboratory evaluation should include a complete metabolic profile and blood count. Addressing electrolyte imbalance and evidence of infec-

tion are especially important. Toxicology for therapeutic and illicit substance use and abuse is essential in the primary search for the etiology of status.

4. It is essential that first responders ensure a patient's airway and adequate respiration. Circulation also is addressed and maintained for primary life support. The initial approach to treatment should include administration of 1 ampule of D50W (glucose) to limit potential consequences from hypoglycemia. Especially in diabetics, this common cause of status epilepticus can lead to permanent damage if not treated aggressively. Similarly, folic acid and thiamine are administered (especially in chronic alcohol abusers) to off-set nutritional deficits. The initial drug treatment should include a benzodiazepine. Two to 4 mg of IM midazolam, 2–4 mg of IV lorazepam, or 5–10 mg of IV diazepam should be given. This should then immediately be followed by maintenance ASDs. Twenty milligrams per kilogram of IV fosphenytoin has been the usual approach in adults with focal seizures unless there are extenuating circumstances that militate against its use.
5. The EEG has one of the most important roles in the management of convulsive status epilepticus. Once generalized convulsive status epilepticus has been recognized, an EEG is needed in order to assess the response to therapy. Continuous EEG or quantitative EEG is a valuable tool that is essential in detecting ongoing electrographic seizures and status epilepticus that may often occur after the motor manifestations of convulsions have ceased.

Clinical Pearls

1. Convulsive status epilepticus is serious and a potentially life-threatening medical emergency.
2. The operational definition of status epilepticus applies to seizures that are greater than 5 min in duration, reflecting the emergent need for treatment due to the likelihood of continued seizure.
3. The evaluation of patients presenting with convulsive status epilepticus should include assessments for illicit substance, complete blood count and metabolic profile, urinalysis, chest X-ray, EKG, brain imaging, and antiepileptic drug levels if the patient has a history of epilepsy.
4. All individuals who manage people with status epilepticus should have a clear well-delineated protocol. This is essential so that an established course of action exists for patients who present with status to ensure that no time is lost.
5. The three most crucial prognostic factors determining the outcome from status epilepticus reflects the underlying etiology, the speed of antiseizure treatment, and the age of the individual. Older aged individuals with status epilepticus frequently have a symptomatic cause, possess a more limited reserve to recover due to comorbidities, and have a higher mortality rate.

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Chapter 37
Status Epilepticus Non-convulsive

Joseph I. Sirven

Case Presentation

A 69-year-old female was brought to the emergency room after her family had not received regular communication from her after several days. She was awake upon examination, but her family reported that she was "not right." She appeared very emotional. She was appropriately responsive to simple questions, but at times she appeared to be talking to herself, was actively hallucinating, and was acting as though there were other people in the room that were talking with her. The patient had no prior history of similar behavior. She had been independent and had reported no other recent problems. In the emergency room her vital signs, laboratory studies, and temperature were all within normal limits. She was attended to by the chief of medicine who wanted to transfer the patient to an inpatient psychiatric facility due to his belief that this must be the presentation of a dementia that was likely Alzheimer's disease. The following EEG was obtained (Fig. 37.1):

Clinical Questions

1. What is the likely diagnosis based on this EEG?
2. What are the most probable causes for this condition?
3. What should be the initial diagnostic study in these types of cases for evaluation?
4. What treatment should be initiated?
5. What maintenance treatment should be continued and what is the prognosis?

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W.O. Tatum et al. (eds.), *Epilepsy Case Studies: Pearls for Patient Care*,
DOI 10.1007/978-3-319-01366-4_37,

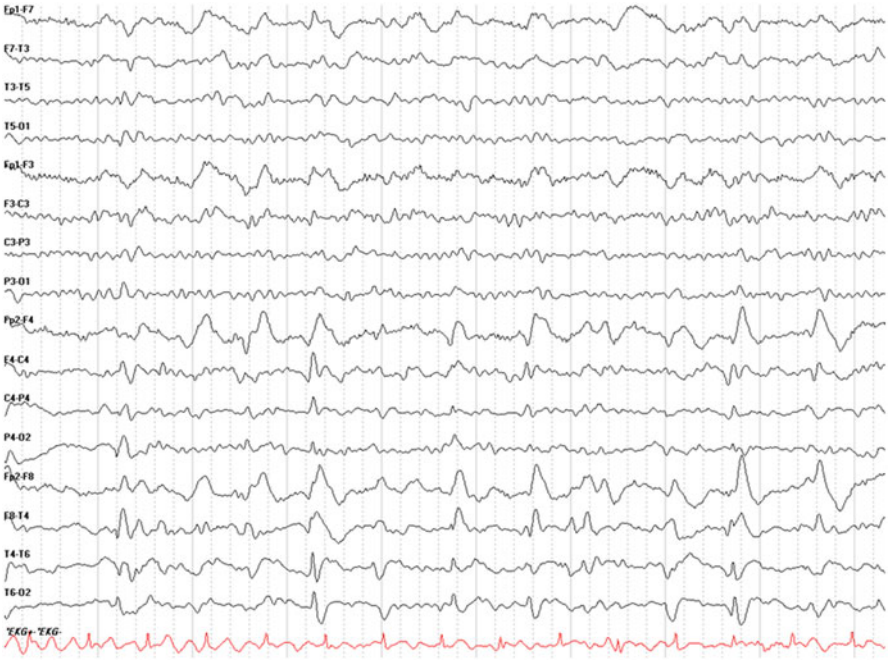

Fig. 37.1 EEG demonstrating continuous 1 Hz repetitive epileptiform discharges predominately in the right hemisphere maximal in the temporal region

Diagnostic Discussion

1. The EEG in this case reveals the presence of an ongoing right hemispheric electrographic seizure. Ongoing right hemispheric epileptiform discharges are seen that are maximal in the right temporal region (Fig. 37.1). This finding was present on every page in the EEG recording with waxing and waning the electrocerebral activity that was consistent with non-convulsive status epilepticus (NCSE). Non-convulsive status epilepticus is a condition of ongoing seizures unaccompanied by visible motor symptoms. The EEG is the diagnostic test that is required to confirm the diagnosis.
2. Cerebrovascular disease is the most common cause of non-convulsive status epilepticus in older adults and merits exclusion. Other common causes of non-convulsive status epilepticus in an older adult may include recent infections, such as pneumonia or urinary tract infection; however, it may also be due to a recent change in medication. Antibiotics, antidepressants (i.e., bupropion), and analgesics (i.e., tramadol) are prescription medications that may be associated with non-convulsive seizures. In younger individuals an association with illicit substances such as neurostimulants including cocaine, amphetamines, ecstasy, and heroin should be considered. Even alcohol withdrawal may produce a similar a hyperexcitable state.

3. Initial diagnostic studies in these individuals should include the EEG when there is a change in baseline mental status or behavior. Both EEG and an imaging study are essential to exclude neoplastic or cerebrovascular etiologies. In the absence of any structure abnormality, an EEG should be obtained to address the possibility of NCSE, which is quite common in the older adult population.
4. The treatment that should be initiated includes administration of a benzodiazepine such as lorazepam, midazolam, or diazepam. This should be followed by fosphenytoin or other primary AED. Continuous EEG monitoring should be obtained until the patient returns to their baseline function and the seizures have been successfully terminated.
5. Maintenance AED therapy should be subsequently maintained. The choice of agent will depend upon the individual patient profile, other coadministered medications, and the underlying cause of the status epilepticus. These individuals should be maintained on medication for a minimum of 2 years unless there is a clear provocation by a reversible cause that can be accounted for. In the latter case, avoiding the provocative factor may suffice for ongoing treatment once the patient has recovered.

Clinical Pearls

1. Individuals, particularly older ones, who present with delirium or a change in their level of consciousness, should be considered for non-convulsive status epilepticus early in the differential diagnosis, as this is a condition that can be rapidly treated and reversed.
2. Imaging studies, reviews of recent medications, and toxicology studies need to be performed in order to rule out and correct identifiable causes of non-convulsive status.
3. Continuous EEG monitoring should be performed early when non-convulsive status epilepticus is identified.
4. Removing the offending cause or trigger of non-convulsive status epilepticus should be performed for reversible comorbidity. Eliminating infection and avoiding illicit substances that may have caused the non-convulsive status may be sufficient treatments. If there is more structural reason or rationale for the non-convulsive status, then ongoing maintenance therapy will be necessary to prevent future seizures.
5. Non-convulsive status epilepticus can be associated with significant mortality, particularly in older adults. Delays in diagnosis are common and in one study, the delay lasted for days before NCSE was diagnosed and treated.

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Chapter 38
SUDEP and Cardiac Arrhythmia

Joseph I. Sirven

Case Presentation

A 19-year-old male had drug-resistant epilepsy and recurrent focal and generalized seizures. Trauma was reported in early childhood after he was struck by an automobile at the age of 5. This resulted in significant traumatic brain injury and cognitive impairment. In addition, daily, nocturnally predominant, recurrent seizures became noted that were refractory to multiple ASDs. MRI of the brain revealed evidence of prior trauma (detail). EEG demonstrated diffuse slowing. Video EEG monitoring was ultimately performed though a referral for epilepsy surgery evaluation was not pursued (Fig. 38.1).

During his course of treatment, his grandparents were unable to awaken the patient from sleep one morning. The emergency medical system was subsequently activated. He was found unconscious face down and in the prone position. Upon examination clinical response or vital signs were present. An EKG demonstrated asystole prompting unsuccessful treatment of cardiopulmonary arrest. He was pronounced dead early in the morning while still in his bedroom. Retrospectively, he had always been adherent to his AED regimen of phenytoin, levetiracetam, and lacosamide. At autopsy, no underlying cause of death was evident overtly, and seizure was not suspected. Toxicology revealed a phenytoin level of 15 mg/dL and no substances were recovered to explain his death.

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W.O. Tatum et al. (eds.), *Epilepsy Case Studies: Pearls for Patient Care*,
DOI 10.1007/978-3-319-01366-4_38,

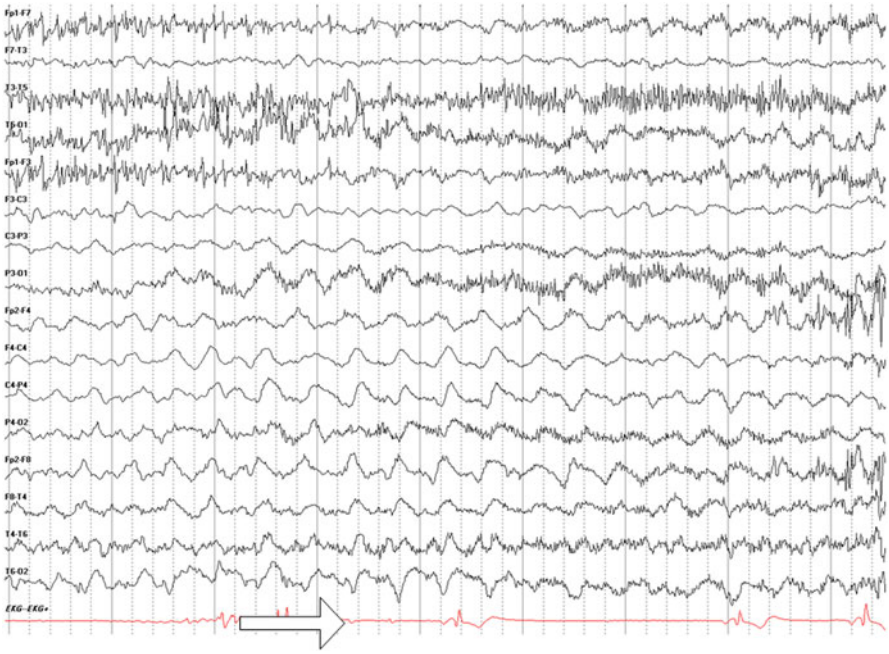

Fig. 38.1 Ictal EEG during diagnostic vEEG monitoring that demonstrated ictal bradycardia (*arrow*)

Clinical Questions

1. What is the most likely cause of death?
2. What does the ictal EEG from his previous epilepsy monitoring session suggest as the possible etiology?
3. What pathological mechanisms underlie sudden death in epilepsy?
4. What are the risk factors for this patient?
5. How should other individuals with seizures and epilepsies similar to this patient be counseled regarding the risk of death in epilepsy?

Diagnostic Discussion

1. The likely cause of death in this case is sudden unexpected death in epilepsy (SUDEP). SUDEP is the most common cause of epilepsy-related death. The risk of death in people with epilepsy is more than 20 times greater than that of the general population.

2. The ictal EEG suggests that the patient has previously demonstrated ictal bradycardia and a propensity to cardiac arrhythmias during seizures. This suggests that a cardiac mechanism may be implicated in the cause of death. Cardiac arrhythmias are well known to occur with seizures and can present in any number of varieties, including ictal tachycardia, which is the usual cause, as well as ictal bradycardia, or even asystole, as in this case. In addition, more malignant ventricular dysrhythmias may occur and exist as an important component of SUDEP.
3. The mechanisms that underlie SUDEP include the possibility of fatal cardiac arrhythmia, suffocation, and neurogenic pulmonary edema. The exact cause of death in these cases is still yet to be fully elucidated, but a number of cardiorespiratory mechanisms may be responsible independent of clinical seizures or status epilepticus at the time of death.
4. The most commonly recognized and predictable risk factor for SUDEP is the presence of uncontrolled seizures. Seizure-related risk factors also include the onset of epilepsy at an early age, ongoing frequent seizures, frequent generalized tonic–clonic seizures, and a long duration of epilepsy. Neurological features that are risks for SUDEP include an IQ less than 70 and the presence of a significant neurological abnormality. Clinical studies have found an increased risk with fluctuation in AED administration, subtherapeutic AED levels, AED polytherapy, nocturnal seizures, and patients who require a vagus nerve stimulator.
5. Numerous advocacy groups and consensus opinions recognize that individuals with epilepsy and their caregivers want to know about the risk of death in epilepsy. It is important to present the information in an appropriate light, given the impracticality limits of our control over death in epilepsy. However, it is information that may serve to help reinforce the seriousness of the condition relative to adherence to treatment while avoiding overt coercion of patients for a specific form of therapy. Rather, it should be noted from the initial visit that uncontrolled seizures carry a real, yet small risk of morbidity and mortality.

Clinical Pearls

1. Seizures, especially when they are drug-resistant, can result in sudden unexplained death in epilepsy.
2. Recurrent seizures are the most important risk factor for SUDEP.
3. Patients with epilepsy may experience serious cardiac rhythm disturbances during seizures. Cardiac pacemakers may be required for arrhythmia when seizures are not controllable.
4. All patients and their families have the right to be informed about the risk of SUDEP to ensure that they are aware of the seriousness that is associated with seizures and its treatment.

5. Epilepsy surgery should be considered when seizures are uncontrolled. Patients have a greater likelihood of averting the risk of SUDEP if they achieve seizure freedom.

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Chapter 39
Investigational Treatment for Epilepsy

William O. Tatum IV

Case Presentation

A 26-year-old right-handed female had drug-resistant localization-related epilepsy. She experienced six febrile seizures beginning at 6 months of age with her first afebrile seizure at 11½ years. Seizures were manifest as an abrupt indescribable feeling evolving to a "focused" stare, impaired consciousness, and inability to speak for 2 min. A rare convulsion would occur. Recurrent seizures were 1–3/week. MRI brain demonstrated left mesial temporal sclerosis. PET had left temporal hypometabolism. EEG revealed left frontotemporal sharp waves and prior video-EEG monitoring captured two left hemispheric seizures. A Wada test was performed. Left hemispheric language function was present. Memory was impaired on the left relative to the right (recall with 7/10 vs. 9/10 picture recall right). She was told of a risk for verbal memory deficit with temporal lobectomy was refused. After failing six ASDs, she was implanted with a responsive neurostimulator as part of a clinical trial (Fig. 39.1). Unfortunately, she had less than a 25 % reduction of clinical seizures. Upon reevaluation 3 years later, repeat video-EEG demonstrated left hemispheric seizures again. A repeat Wada test had a similar finding. She continued to refuse surgery. A minimally invasive investigational protocol was offered.

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W.O. Tatum et al. (eds.), *Epilepsy Case Studies: Pearls for Patient Care*,
DOI 10.1007/978-3-319-01366-4_39,

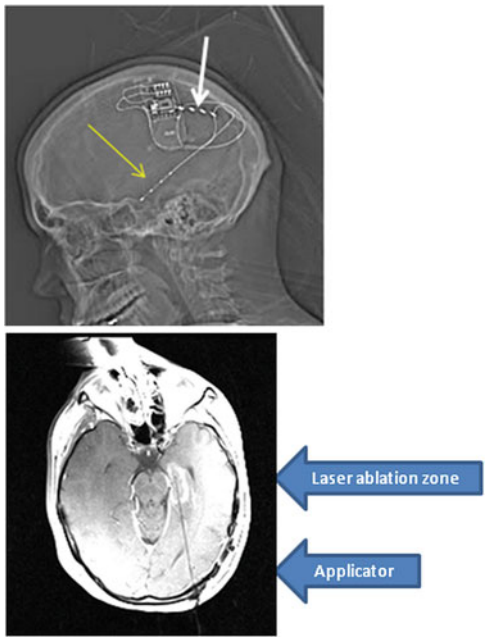

Fig. 39.1 (**a**) Lateral skull X-ray with a depth electrode (*yellow arrow*) and subdural strip (*thick white arrow*) connecting the RNS at the suspected sites of seizure onste and (**b**) thermal "damage estimate" in the left mesial temporal region. Thermal application 12 W for 120 s (first application) and 153 s (second appliation) with epicenter reaching 97.7 °C

Clinical Questions

1. What standard AED treatments exist for epilepsy?
2. What is the problem of drug resistance and treatment?
3. When is it appropriate to seek investigational treatments in epilepsy?
4. How do neurostimulation and surgical failure or refusal interface?
5. What investigational surgical options are there?

Diagnostic Discussion

1. The standard antiepileptic drug (AED) options in the treatment of epilepsy are the mainstay of therapy in more than 90 % of patients. The "old" ASDs included phenobarbital, phenytoin, primidone, ethosuximide (absence only), carbamazepine, and valproate. The "new" ASDs include gabapentin, lamotrigine, topiramate, tiagabine, oxcarbazepine, zonisamide, levetiracetam. The "newest" ASDs include pregabalin, rufinamide, vigabatrin, ezogabine, clobazam, and parampanel. Because of improved tolerability and less drug-drug interactions, the newer ASDs may replace the "older" ones as first-line treatment. Ensuring the correct diagnosis, correct AED and dose, and a proper lifestyle are the foundation to exclude "pseudoresistance." When these caveats are met, once drug-resistance

is encountered, it is unlikely that additional trials of old or new AED use will result in seizure freedom.

2. Seizure freedom without side effects is the goal for every patient with epilepsy. Seizure free means no seizures for three times the longest inter-seizure interval or more than 12 months, whichever is the longer time period. Even infrequent seizures that continue despite ASDs create higher depression rates for patients. Cognitive and memory impairments caused by seizures and by AED adverse effects are common and directly impact and impair the overall quality of life of the individual person. The long-term consequences of AED therapy can involve many adverse effects, including weight gain, hair growth, neuropathic symptoms, osteoporosis, and cerebellar symptoms, in addition to teratogenetic complications. Ongoing seizures are associated with a reduced lifetime income and increase in health care utilization. A greater risk of morbidity and even mortality with sudden unexplained death being the most common feared complication of patients with epilepsy may occur.
3. For patients experiencing persistent seizures, less commonly used ASDs include ethotoin, methsuximide, mephobarbital, acetazolamide, felbamate may be considered in addition to other FDA-approved ASDs. These agents have inferior efficacy, poor tolerability, and adverse effects (i.e., felbamate) that make them less useful choices for those with drug-resistant epilepsy when other options exist. Investigational agents may find a role in treating epilepsy at some point. Those on the horizon include eslicarbazepine, brivaracetam, carisbamate, stiripentol, and ganaxalone among others. The decision to enroll in an investigational trial is dependent upon patient interest, availability of a trial, and an ethical interest of the physician to enroll the patient at an appropriate time.
4. Our patient refused epilepsy surgery due to personal conviction and fear of a surgical complications involving memory loss. While a relative risk, the consequences of uncontrolled seizures include morbidity and mortality. An asymmetric Wada has an uncertain prediction in the degree of post-operative verbal memory decline. Despite recommendations to the contrary, she continued to refuse surgery. Consequently, neurostimulation was discussed. Vagus nerve stimulation (VNS) is an adjunctive treatment to ASDs and may reduce seizures; however, less than 5 % become seizure free. She opted instead for a clinical trial involving the responsive neurostimulator. This system involves a skull-based generator designed to deliver an electrical stimulation to 1–2 electrodes that are strategically placed at the site of anticipated seizure onset. Depth and subdural strip electrodes respond to a specified ictal rhythm on intracranial EEG that is "learned" by the programmable generator. Unfortunately, our patient did not have an appreciable response and was discontinued from the study in favor of a newer treatment.
5. Some patients are interested in participating in research trials. The chance to participate in the latest "cutting edge" treatment bears an opportunity to become seizure free that is tantalizing after multiple disappointments from ASDs. Most patients seek these avenues when they are deemed nonsurgical; however, some patients, such as ours, are reluctant for personal reasons. A new trial using the

application of a diode laser housed in a coaxial saline cooling catheter became available to our patient and she wished to enroll. This trial evaluated mesial temporal sclerosis and drug-resistant epilepsy. The minimally invasive procedure uses a burr hole to place a continuous-wave diode laser probe within a 1.5 Tesla MRI scanner to ablate soft-tissues using real-time thermal imaging. This creates a localized region of coagulation necrosis in the amygdala and hippocampus. The desiccation is controlled to 1 mm of damage. Our patient underwent the procedure and had no complaints the next morning. She has had no further seizures 1 month after the procedure.

Clinical Pearls

1. Investigational treatments include ASDs as well as neurosurgical procedures.
2. Medication failures are not defined by "old," "new," or even the "newest" ASDs, nor are they mitigated by those less commonly used. Rather, they are defined by the number of appropriate drug exposures with a working definition that prompts consideration of nonmedical therapies.
3. Mainstream surgical considerations are not acceptable risks for every patient with the degree of invasiveness balanced by accepting less invasive (surgical) therapies even when they are investigational.
4. "Laser" treatment of epilepsy is an emerging area of interest for patients with localization-related epilepsy and well-circumscribed pathophysiology.

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Chapter 40
Alternative Medicines in Epilepsy

Joseph I. Sirven

Case Presentation

A 24-year-old female patient has a known diagnosis of Localization-related epilepsy. Her focal seizures were ultimately controlled using an antiepileptic drug combination of levetiracetam and carbamazepine. The patient was brought to the emergency room 1 day by her mother when she noted that her daughter had "not been herself." On examination, the patient was confused and did not answer questions appropriately. She appeared to be awake and her neurological examination was without focal features. When asked questions, she parroted the words of the questions back to the examiner. According to her mother, she was compliant with her antiepileptic medications. There had been no other recent major changes in her activities, other than taking the ginseng extract that she had obtained from a coworker. Her coworker had apparently been growing natural remedies at home to use as medicinal agents. Our patient took the extract in an effort to improve her memory performance. In addition, she had obtained cannabis because she thought that it helped improve her epilepsy. When she arrived in the emergency department, laboratory testing revealed no significant abnormalities in her complete blood count and metabolic profile. The levetiracetam level was found to be within the ranges supplied by the laboratory. The carbamazepine level was low at 2 mg/dL. Neuroimaging studies were unremarkable. A urine drug toxicology screen was positive for cannabis. Subsequently, an EEG was obtained (Fig. 40.1).

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W.O. Tatum et al. (eds.), *Epilepsy Case Studies: Pearls for Patient Care*,
DOI 10.1007/978-3-319-01366-4_40,

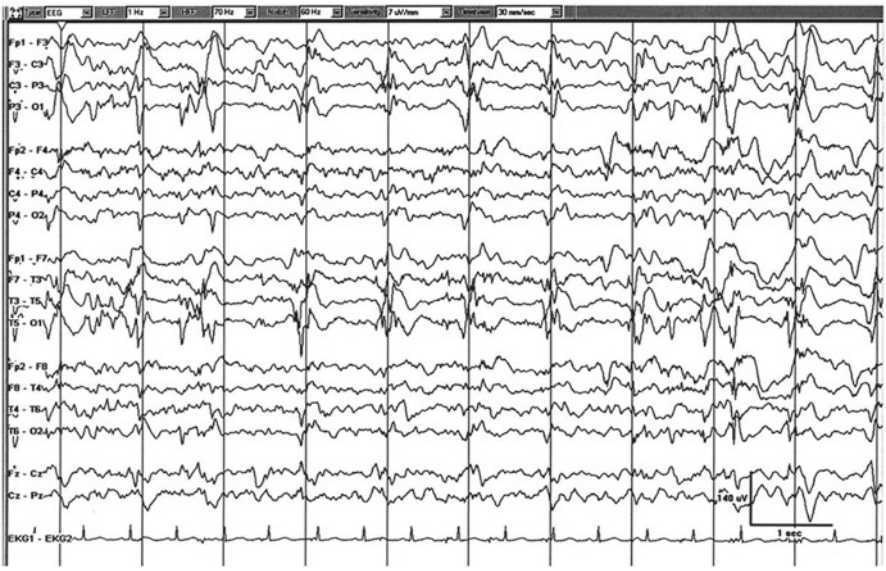

Fig. 40.1 EEG demonstrating periodic lateralized discharges emanating from the posterior quadrant of the left hemisphere associated with a diffusely slow background activity

Questions for Discussion

1. What does the EEG demonstrate?
2. What is a complementary and alternative medicine (CAM)?
3. Is there any evidence to use CAM for epilepsy?
4. Are there any concerns with CAM use?
5. What is the role of cannabis in epilepsy management?

Discussion

1. The EEG figure demonstrates ictal periodic lateralized discharges emanating from the left hemisphere. This was associated with non-convulsive status epilepticus. The low carbamazepine level was suspected to be involved as a primary explanation.
2. CAM is defined as a group of diverse medical and health care systems, practices, and products that are not generally considered part of traditional Western medicine by the National Center on Complementary and Alternative Medicine (NCCAM; formally known as the Office of Alternative Medicine). The NCCAM is a US governmental agency that evaluates CAM and is one of many centers/institutes that comprise the NIH within the Department of Health and Human Services. Many individuals with epilepsy may seek out the use of "complementary"

Table 40.1 CAM treatments

CAM treatments
Herbals/botanicals
Ayurvedic care
Chiropractic care
Biofeedback
Yoga
Homeopathy
Spirituality

or "alternative" treatments to improve their outcomes. CAM treatment can include a number of different compounds and approaches (Table 40.1). Treatment with hormones, oxygen therapy, nutrition, and vitamins may be encountered in addition to Asian and traditional Chinese medicine, herbal and botanical treatments, and other homeopathic compounds that may be used by patients. Stress relief practices such as exercise, reiki, chiropractic, meditation, ayurvedic care, and acupuncture may be used among others, and can carry ramifications to treatment.

3. There have been no clear randomized control studies that have evaluated the usefulness of CAM for epilepsy. However, a Cochrane Review has found that stress relief through either yoga or acupuncture may have theoretical implications for benefit, yet there is a lack of studies that sufficiently establish definitive proof of benefit.
4. Some CAMs can be concerning. Some individuals may harbor the false belief that if they take a CAM, they can stop their antiseizure drugs. In the case above, the individual stopped carbamazepine with the goal of using cannabis and ginseng to improve her epilepsy with a "natural" treatment. Unfortunately, this resulted in a seizure emergency not uncommonly seen with non-adherence to the treatment regimens prescribed by one's physician. Moreover, some alternative therapies can be proconvulsants or possess drug–drug interactions. For instance, ginseng and similar herbs may act as proconvulsants. However, different portions of the same plant may be protective. Using CAM should be disclosed to one's physician to ensure that appropriate treatment and counseling are able to be made.
5. Although epilepsy is frequently cited as one of the conditions that the use of cannabis may benefit, there are no randomized controlled trials demonstrating evidence to refute or support this claim. There is basic research assessing tetrahydrocannabinol and its potential impact on antiepileptic agents. However, there are no definitive clinical trials in humans.

   Some epidemiological studies have suggested that cannabis can be protective against epilepsy. However, because cannabis is not a regulated drug, any filler or additive can be added to cannabis and can potentially cause harm. The question still remains as to the role of cannabis in epilepsy treatment. In this case, counseling the patient should include a discussion about ceasing cannabis use and maintaining compliance with antiseizure drugs as directed by the physician.

Clinical Pearls

1. It is important to be supportive of the concept of alternative and complementary medicine techniques, especially if it poses little risk to the therapies that are being prescribed.
2. Stress reduction is always beneficial for individuals with epilepsy. Biofeedback, yoga, and spirituality methods are appropriate choices.
3. Switching from traditional antiseizure drugs to rely upon alternative medicines as the sole treatment for epilepsy is a recipe for problems. Although cannabis has achieved "grassroots" popularity, there is no evidence to currently support or refute its use for epilepsy. Caution must be undertaken, given that there is no regulation as to how cannabis is distributed or what ingredients are added to it. In addition it is considered an illegal substance in most states and is subject to legal prosecution. Always disclosing to one's physician the full variety of treatments that can be utilized is the best means to minimize unexpected complications.

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W.O. Tatum et al. (eds.), *Epilepsy Case Studies: Pearls for Patient Care,*
DOI 10.1007/978-3-319-01366-4, © Springer Science+Business Media New York 2014