Epilepsy Case Studies

Pearls for Patient Care

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

Second Edition

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This book is dedicated to our patients and their families who have taught us so much about epilepsy and about life.

DKWILY

Foreword

What can we learn from the stories about a single patient with epilepsy? Consider the case of a young reporter who experienced "a month of madness" and was ultimately discovered to have anti-NMDA receptor encephalitis that uncovered the importance of autoimmune epilepsies. Consider genetics and rare diseases that have come to define populations with limited number of patients. Consider the impact from the unfortunate experience when a patient ultimately succumbs to epilepsy suddenly and unexpectedly is then impossible to "study" given ethical constraints and finality of the process. Consider the patient who has a rare disorder and epilepsy, experiences a rare side-effect, or becomes seizure-free with their ninth antiseizure medication (ASM). Or when surgery becomes successful after failure of the same ASM usage. Consider the one case of Henry Molaison ("H.M."), who underwent bilateral temporal lobe surgery for drug-resistant epilepsy, and how this changed all subsequent surgeries from that time onward to avoid making a similar mistake.

The chapters in this book represent real people and real-life situations that had consequences both good and bad depending upon their individual situation. The intent of presenting these patients in a case-based format is designed to stimulate the same deductive reasoning on a personal level when we see patients in the clinic. The utility 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 interpretation of these studies is essential for the neurologist and foundational for the epileptologist. Following the clinical scenario composed of a wide variety of epilepsy cases, questions are posed to organize the reader's thoughts in addressing the pertinent features of each case. Questions that include commonly asked ones such as, "How does this test help us with the diagnosis?" and "What is the relationship of the seizures to the patient's condition?" Other 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 the clinical course and evaluation. 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 referenced. Unlike a textbook, these cases include a few of the more pertinent

articles that the reader can refer to obtain an overview of the topic and search for an expanded bibliography, if they so desire.

We learn from every patient. In the end, it is the individual report that "restores the human subject at the center of attention as the suffering, afflicted, fighting, human subject… only then do we have a 'who' as well as a 'what', a real person, a patient, in relation to a disease-in relation to the physical".* Our take-home messages are encapsulated in the form of clinical pearls. These "bullets" of information form the basis of our understanding of the case scenarios presented. Furthermore, they guide our decision-making in an approach to treatment for an individual patient. 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. Additionally, our patients' case histories are the best tools to successfully guide us toward the correct approach to different clinical scenarios; the overuse of "tests" will never replace the clues that our patients give us. 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. The second edition of *Case Studies in Epilepsy* will aid in selecting the approach to a clinically based problem list. Cases include the newly diagnosed to drug-resistant epilepsy, epilepsy from unknown causes to seizures caused by a brain tumor, infants and the elderly with epilepsy, diagnostic dilemmas, and treatment challenges. Novel associations involving genetics and autoimmunity are addressed. Surgical approaches in the uncontrolled person with epilepsy include non-medical treatment options, such as resective and laser surgery, neuromodulation, dietary control, alternative medicine, and investigational approaches. The cases in *Case Studies in Epilepsy* encompass a broad range and heterogeneous group of the epilepsies from those with genetic to structural-metabolic to those with unknown causes. Compiling these cases has been fun; we remember the people who taught us much about patient experiences and about the impact upon a full productive life. Today, even in the most highly regarded academic centers, professors from their subspecialties will be heard saying, "I remember the case of Mrs. Smith and will never forget it."

William O. Tatum IV

*O. Sacks The man who mistook his wife for a hat. Summit books. Simon & Schuster New York; 1999.

Acknowledgment

I would like to acknowledge my gratitude to my colleagues at the Mayo Clinic for both the opportunity to work alongside them and to learn from them. This multi-authored enterprise-wide work has been compiled by many outstanding clinicians, educators, and researchers, who freely and generously volunteered their precious time to contribute to this work, and serves as a testimony to their dedication to the field of epilepsy and to their colleagues. This book is about 50 people whose lives took a different course after they experienced seizures. The stigma and painful lack of predictability experienced by patients, friends, and families is something most of us will hopefully never know. The cases described in this book are presented in a didactic fashion, but lack the emotional content behind each case to limit the real impact that written text is too shallow to appreciate.

One of my first mentors taught me that patient care is the most noble aspect in the practice of neurology. Those who cannot work with people…teach or research sometimes in an effort to avoid patient care. What is missed is the humanity of suffering and the excitement of clinical success. We must always remember that it is people who are behind the symptoms of their illness and that treatment begins with the compassion displayed by a personal human touch. When we live our professional lives by the words of William and Charles Mayo, "The needs of the patient come first," we bring to light and acknowledge what is truly important for the focus in the practice of Medicine.

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Epileptic Spasms

1

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 moreso 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 significant reduction in frequency, despite dose increases to 20 mg/kg/d.

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 3600 grams. She was discharged from the hospital at 2 days of age and was well without incident until 7 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 arm and tended to use it less than her right arm. Sensory examination revealed that she had symmetrical withdrawal to stimulation. No pathological cerebellar functions or reflexes were evident. Interictal EEG (Fig. 1.1) and brain MRI (Fig. 1.2) were also subsequently obtained.

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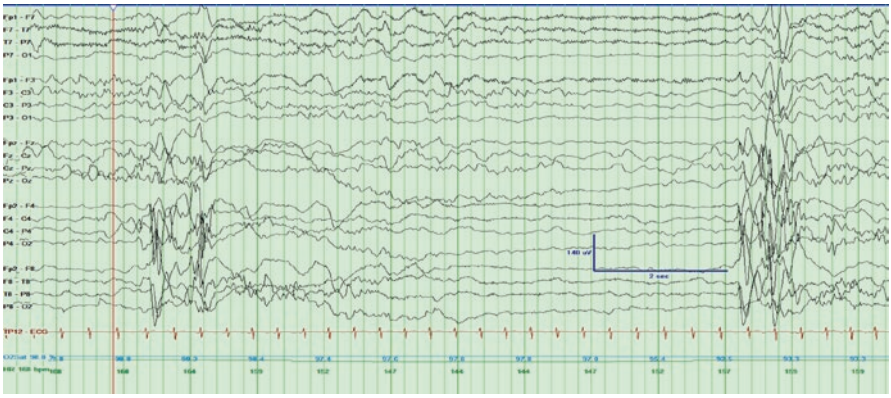

Fig. 1.1 Interictal EEG demonstrating right frontotemporal epileptiform discharges. Sensitivity 10 microvolts/mm, filter settings 1 and 70 Hz, display speed 30 mm/sec

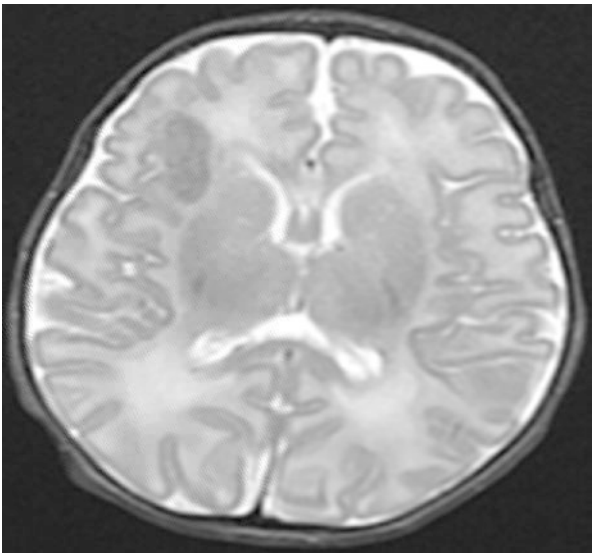

Fig. 1.2 Coronal T1 MRI of the brain at 6 weeks of age. Note the hypointensity in the right frontotemporal region involving the insular cortex

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 most seen commonly in the first year of life and characteristically occur in clusters, as in this child's case [1]. 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 (d) 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. 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 T2 hypointensity in the right anterior insular cortex. This is most likely due to a focal malformation of cortical development. In early infancy, focal cortical dysplasia is hypointense on T2. Due to ongoing myelination, such malformations can be very challenging to visualize between 4 and 24 months. After 2 years, focal cortical dysplasia 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.
4. Her interictal EEG pattern showed bursts of 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 hypsarrhythmia (note the absence of high voltage EEG).

   A clinicopathological classification system has been proposed, which divides these lesions into the following groups [2]:
   - FCD Type I: abnormal cortical layering that either compromise 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), and FCD Type IIId (other lesion acquired early in life).
- FCD Types II and III may appear morphologically on the brain MRI. FCD Type I have 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. One recent study documented improved short-term outcome regarding spasm resolution with combination hormonal therapy with vigabatrin [3]; however follow-up after 18 months showed no difference in development between the two groups [4]. She was treated with vigabatrin 140 mg/kg/d and became seizure-free for 7 months. 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 malformation of cortical development. Focal resections have been effective in patients with ES as it was in her case rendering her seizure free [5]. The pathology was consistent with FCD IIA (without balloon cells).

Pearls of Wisdom

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.
3. The occurrence of focal ES with co-existent focal seizures or a focal abnormality on the neurological examination or EEG suggests the presence of a focal lesion.
4. Focal malformations of cortical development 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.
5. A referral for an epilepsy surgical center for assessment should be considered in a young child with drug-resistant seizures who has failed two antiseizure medications due to a lack of efficacy. Such referral is urgent if there is evidence of developmental regression.

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Neonatal Seizures and Metabolic Epilepsies

2

Anthony L. Fine and Lily C. Wong-Kisiel

Case

A 2-day-old girl was transferred for further evaluation of seizures. She was born at term to non-consanguineous parents with pregnancy complicated by group A beta-hemolytic streptococcus which was adequately treated with antibiotics. She was born via vaginal delivery, and Apgar scores were 8 and 9 at 1 and 5 min, respectively. There were no complications at delivery, and she appeared well on day of life 1 in the newborn nursery. On day of life 2, she began having stereotypic jerks of her upper extremities. On examination she was non-dysmorphic and noted to be diffusely hypotonic and hyporeflexic. She was noted to have quick, isolated jerks of her left and right upper extremities as well as frequent hiccups. She would have intermittent pauses in her breathing. She had depressed suck, rooting, and Moro reflexes. There were no abnormal skin findings, and she had no organomegaly.

She underwent evaluations including lumbar puncture, labs, EEG, and brain MRI and MR spectroscopy (MRS). The EEG recording showed a suppression-burst pattern with generalized burst activity alternating with generalized suppression, which lasted up to 10 s (Fig. 2.1). Generalized discharges were associated with body jerking, consistent with myoclonic seizures. The brain MRI showed hypoplasia of the corpus callosum and an immature sulcation pattern. The MRS showed an elevated glycine peak (Fig. 2.2). The serum glycine level was 2315 mmol/L (reference 232–740 mmol/L), CSF glycine was 370 umol/L (reference 5–38 umol/L), and the CSF/serum glycine ratio was 0.16 (reference < 0.03).

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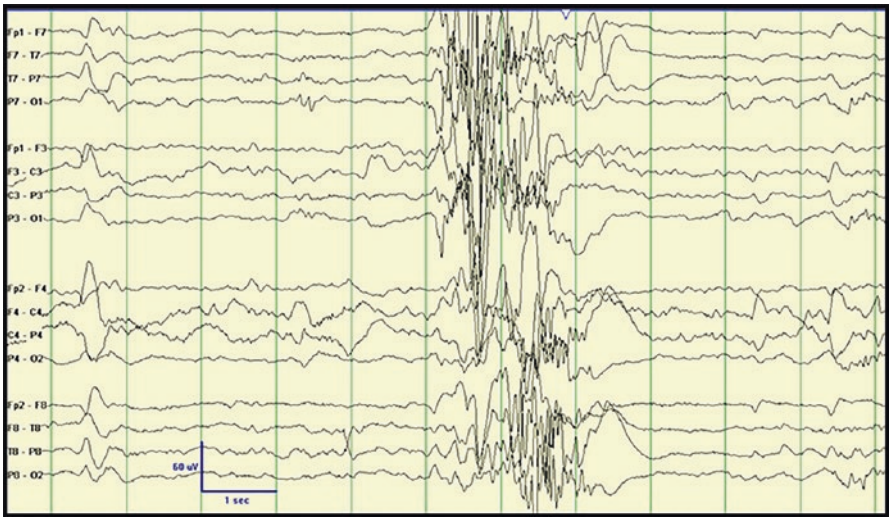

Fig. 2.1 EEG in bipolar montage demonstrating periods of EEG suppression and high amplitude generalized discharge (suppression-burst pattern)

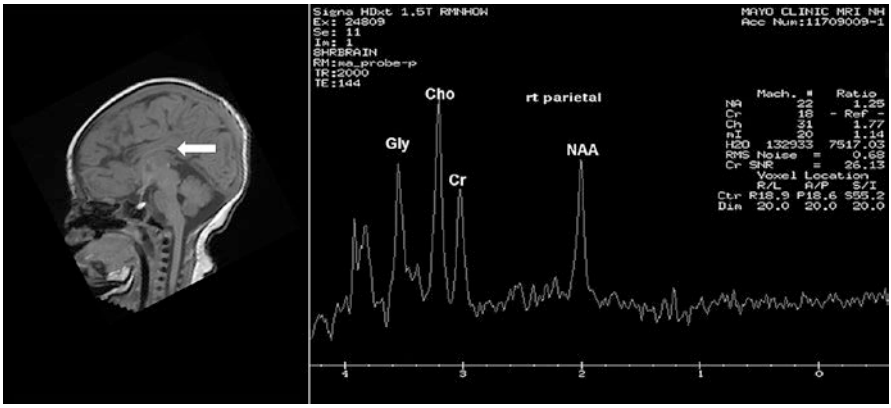

Fig. 2.2 Left panel: sagittal T1 brain MRI demonstrating hypoplastic corpus callosum (white arrow) and immature sulcation pattern. Right panel: MR spectroscopy with elevated glycine peak. *Cho* choline, *Cr* creatine, *Gly* glycine, *NAA* N-acetylaspartate

Questions

1. What is the differential diagnosis for a neonate with seizures and a suppression-burst pattern on EEG?
2. In what conditions can an elevated CSF-to-serum glycine ratio are seen, and what additional findings and/or studies can be helpful?

3. How would you classify this patient's seizures and epilepsy?
4. How would you treat this disorder?
5. What is the prognosis for this disorder?

Discussion

1. A neonate with seizures and a burst-suppression pattern on EEG suggests a severe encephalopathy, with a hypoxic-ischemic insult, metabolic, or epileptic encephalopathy being the most likely etiologies. The unremarkable pregnancy and birth history with an initially normal presentation would argue against hypoxic-ischemic encephalopathy. The presence of a burst-suppression pattern in a neonate also suggests an epileptic encephalopathy, with early infantile epileptic encephalopathy (a.k.a. Ohtahara syndrome) or early myoclonic epileptic encephalopathy (EME) potentially fitting with this patient's presentation. The clinical features (encephalopathy, myoclonic seizures, hiccups) and study/laboratory findings (suppression-burst pattern on EEG, elevated serum, and CSF glycine with elevated CSF-to-serum glycine ratio) are consistent with the diagnosis of nonketotic hyperglycinemia (NKH).
2. An elevated CSF-to-serum glycine ratio can be seen in several clinical scenarios. This can be seen in neonates with severe hypoxic-ischemic encephalopathy; however, additional findings in the history could include a difficult labor or delivery, low Apgar scores, acidosis, and a depressed newborn. In patients undergoing treatment with valproic acid, an elevated CSF-to-serum glycine ratio can be seen due to inhibition of the glycine cleavage system by valproic acid. This can be seen in metabolic disorders including NKH, pyridoxal 5′-phosphate oxidase (PNPO) deficiency, and organic acidurias. Pyridoxal 5′-phosphate oxidase deficiency most frequently will present as a neonatal epileptic encephalopathy. In addition to an elevated CSF glycine, testing would be notable for low CSF pyridoxal-5-phosphate. There may be a partial response to a trial of pyridoxine; however, treatment would be with pyridoxal 5-phosphate [1]. Elevated glycine levels can be seen in several organic acidurias, including propionic aciduria, methyl malonic aciduria, isovaleric aciduria, and multiple carboxylase deficiency; however, urine organic acid screen is typically normal in NKH and abnormal in these other disorders [2]. An elevated CSF-to-serum glycine is suggestive of NKH but is not confirmatory. Confirmatory testing could include assay of the glycine cleavage enzyme obtained with liver biopsy or by establishment of biallelic pathogenic variants in AMT, GLDC, or GCSH genes [3].
3. The description of the patient's seizures as quick jerks of the extremities associated with generalized discharges would be consistent with myoclonic seizures. The two epileptic encephalopathies to consider in this patient are early myoclonic encephalopathy (EME) and early infantile epileptic encephalopathy (EIEE). In EME, onset is frequently in the neonatal period and can be within the first hours of life with encephalopathy, frequent fragmentary myoclonus, and a suppression-burst pattern on EEG. The etiology for EME is most commonly a

metabolic disorder; however, genetic and structural etiologies have been reported. In EIEE/Ohtahara syndrome, onset is typically within the first 3 months of life and can be within the neonatal period. The presenting seizure type is tonic spasms, which can be generalized but more commonly are asymmetric and focal. NKH can be seen in association with two early onset epileptic encephalopathies, EME and EIEE. On EEG, a suppression-burst pattern will also be seen in Ohtahara syndrome. The most common etiology for Ohtahara is structural abnormalities due to an underlying genetic diagnosis; however this syndrome has been seen in metabolic disorders as well. Given the early onset myoclonus beginning shortly after birth and suppression-burst pattern on EEG, the epilepsy syndrome would be most in keeping with early myoclonic epilepsy secondary to NKH.

4. The treatment of NKH includes therapies aimed at reducing plasma glycine levels and NMDA excitatory signals. There is no cure for NKH, and disease course depends on the form of NKH. Treatment with sodium benzoate does not alter disease course but may improve seizure control [4]. Sodium benzoate conjugates glycine to hippurate which then can be excreted in the urine. Other therapies, including ketamine, dextromethorphan, and felbamate, which are NMDA-receptor antagonists, are used to potentially reduce glycine-induced excitotoxicity [5].
5. The prognosis for NKH is variable but tends to typically be poor. There are several forms including classic, transient, and atypical forms. The classic form of NKH is the neonatal form, with onset within hours to the first week of life, with lethargy, hypotonia, hiccups, and frequent myoclonic seizures. Apneas and respiratory failure can occur, which if untreated will result in coma and death. Survivors of classic NKH invariably have profound neurologic disability and drug-resistant epilepsy (a.k.a. intractable epilepsy), with evolution of burst-suppression pattern often to hypsarrhythmia and infantile spasms followed by Lennox-Gastaut syndrome. Death typically occurs within the first years of life [3, 4].

   Transient NKH is a rare (and controversial) form, which has an identical initial presentation to the classic neonatal form and is felt to be due to immaturity of the glycine cleavage system. Children with transient NKH will have resolution of glycine elevations seen in serum and CSF over time and most frequently have normal neurodevelopment.

   Atypical forms of NKH have heterogeneous age of onset and clinical presentations. In the late-onset form, seizures can be absent; however, other symptoms may include developmental delays, attention deficit disorder, ataxia, movement disorders, and spastic paraparesis. Some individuals will have normal cognition [3].

Our patient's clinical history of early onset myoclonic seizures with burst-suppression pattern on EEG, hypotonia, hiccups, and apneas and laboratory evaluations including elevated serum and CSF glycine levels and elevated CSF-to-serum glycine ratio would be most consistent with the neonatal form of NKH. She was

initiated on sodium benzoate, ketamine, dextromethorphan, and topiramate. She was weaned off the ventilator on day of life 51 and discharged from the hospital at 2 months old. By 3 months of age, she developed infantile spasms. At 18 months, she had profound developmental delay and frequent hospitalizations for her drug-resistant seizures. She passed away at age 3 years due to respiratory failure and decompensation in the setting of illness.

Clinical Pearls

1. In a neonate with encephalopathy and seizures with an unremarkable perinatal course and without other features consistent with hypoxic-ischemic encephalopathy, additional etiologies such as an underlying metabolic or genetic disorder should be considered.
2. In a neonate with an epileptic encephalopathy with a suppression-burst pattern on electroencephalogram, diagnoses to consider include early myoclonic encephalopathy (EME) and early infantile epileptic encephalopathy/Ohtahara syndrome.
3. Nonketotic hyperglycinemia should be strongly considered as a possible diagnosis when findings are consistent with EME, and an evaluation of serum and CSF glycine should be performed.
4. In patients with NKH, the classic neonatal form has poor prognosis in terms of development, drug-resistant epilepsy, and death within a few years of diagnosis. In atypical forms, the disease course may be more attenuated with some individuals presenting with movement disorders and spastic paraparesis.
5. There is no curative therapy for NKH. Treatments are aimed at reducing excitotoxicity associated with excess levels of glycine, as well as, anti-seizure medications for seizure reduction.

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Febrile Seizures

3

Harry S. Abram

Case Presentation

An 18-month-old girl presents to a local emergency room following a 20 min generalized tonic-clonic seizure. She has been an otherwise healthy child with age-appropriate developmental milestones. Upon assessment, in the emergency room, she has a temperature of 103° and an inflamed right tympanic membrane. She was initially irritable and uncooperative. Following ibuprofen, her temperature resolved, and within 60 min, she was cooperative, and she had a normal neurological examination.

Family history is notable for an older brother who had a similar event with a fever and a maternal aunt who developed epilepsy as a young adult. She has received all of her immunizations and has not been on any medications at home. The parents witnessed the seizure and were very frightened by it. Their fears concern further seizures, epilepsy, "brain damage," and death.

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?

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Diagnostic Discussion

1. The International League Against Epilepsy (ILAE) defines a febrile seizure as "a seizure occurring in childhood after one month of age associated with a febrile illness not caused by an infection of the central nervous system, without previous neonatal seizures or a previous unprovoked seizure, and not meeting the criteria for other acute symptomatic seizures."

   This is considered a genetic age-limited seizure disorder in which seizures occur only with fever. This is the most common seizure type 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. In contrast, complex FS are prolonged (>15 min), are focal, occur more than once in 24 h, or are in a neurologically abnormal child and risk factors for developing epilepsy (Table 3.1).

   Febrile status epilepticus, a subgroup of complex febrile seizures with seizures lasting more than 30 min, occurs in about 5% of cases. Seizure may consist of tonic or clonic movements which may be asymmetrical or have brief alterations of awareness.
2. Diagnostic evaluation of a child with a 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 history and clinical examination, with attention to prior treatment with antibiotics and confirmation of appropriate immunizations. Typical meningeal signs such as stiff neck may not be reliably present under the age of 2 years. The overall risk of bacterial meningitis was 0.2% in children with an apparent first simple febrile seizure and 0.6% in children with complex febrile seizure [1]. Beware of an alternative diagnosis if the fever is less than 38.0 °C or if the child is over 5 years of age.

   An EEG is not indicated in a neurologically healthy child with a simple FS. There is no evidence to suggest that laboratory testing is of benefit in the evaluation of the child with a simple FS. These should be obtained only as indicated after appropriate history and careful physical examination. MRI and EEG

Table 3.1 Risk factors for febrile seizures to develop epilepsy

Reported risk factors for developing epilepsy
Complex febrile seizures
Prolonged
Recurrent
Focal features
Abnormal neurological status
1st degree relative with epilepsy

Table 3.2 Risk factors for recurrent febrile seizures

Reported risk factors for recurrent febrile seizures
Age <15 months
1st degree relative with febrile seizures or epilepsy
Low grade fever (<39 °C) at seizure onset
Short duration of fever prior to seizure (<1 h)
Daycare attendance
Complex febrile seizures
Developmental delay

are not typically indicated in simple FS but may be a consideration in children with complex FS [2].

3. After a single FS, the risk of a second is approximately one third, with the majority within 1 year (Table 3.2). This risk may range from approximately 5% up to 80% depending on the number of risk factors.

   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: complex FS, onset younger than 12 months, a family history of epilepsy, abnormal neurological examination, or abnormal neuroimaging [3]. With multiple risk factors, the risk of developing epilepsy by the third decade is 17% versus 2.5% if there are no risk factors [4]. There is no evidence that the use of prophylactic anti-seizure medication with FS can prevent the later development of epilepsy. There currently is no evidence that simple FS cause structural damage to the brain or affect a child's cognition. There has never been a reported death from a simple FS.

   There has been a suggested link of FS to later development of temporal lobe epilepsy, but that exact role remains unclear. Some studies have suggested development of hippocampal sclerosis following a prolonged FS in young infants. Despite retrospective analyses demonstrating that as many as 35% of adults with temporal lobe epilepsy have a history of complex or prolonged febrile seizures in childhood, prospective outcome has been inconclusive and contradictory [5].

4. Despite the frequency of simple FS, long-term daily therapy with an anti-seizure medication is typically not warranted. Although there is evidence that both continuous anti-seizure 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 antiepileptic drugs outweigh the relatively minor risks associated with simple FS [6]. In situations in which parental anxiety is high, seizures are prolonged or recurrent, there is a strong family history of epilepsy, or is there limited access to health care, intermittent use of a benzodiazepine at the onset of febrile illness may be effective in preventing recurrence. The prospective FEBSTAT (Consequences of Prolonged Febrile Seizure) demonstrated that the longer a seizure continues, the less likely they are to stop spontaneously [7]. The importance of pre-hospital treatment protocol with respiratory support and a rescue benzodiazepine is emphasized.

Although antipyretics may improve the comfort of the child, there is no data that this will prevent further febrile seizures [8]. This is useful to note for worried parents, who may blame themselves for not administering adequately antipyretics. A cool bath or washcloth is no longer recommended for febrile children as it may raise core body temperature.

5. Disorders involving voltage-gated ion channels have been of increasing noted in neurological disease. Greater than 300 mutations involving the gene controlling sodium channels (*SCN1A* and *SCN1B*) and *GABRG2* have been implicated in a broad spectrum of mild to very severe epileptic syndromes. These severe 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 and alteration in anti-seizure management (avoiding medications with sodium channel blocking properties) and family counseling.

Pearls of Wisdom

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 anti-seizure medications are not typically recommended. Intermittent use of a benzodiazepine may be appropriate in certain clinical situations either as prophylaxis or as a rescue option.
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 2–3 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 [6, 7]. 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 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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