Chapter 9
Generalized Epilepsy with Febrile Seizures Plus

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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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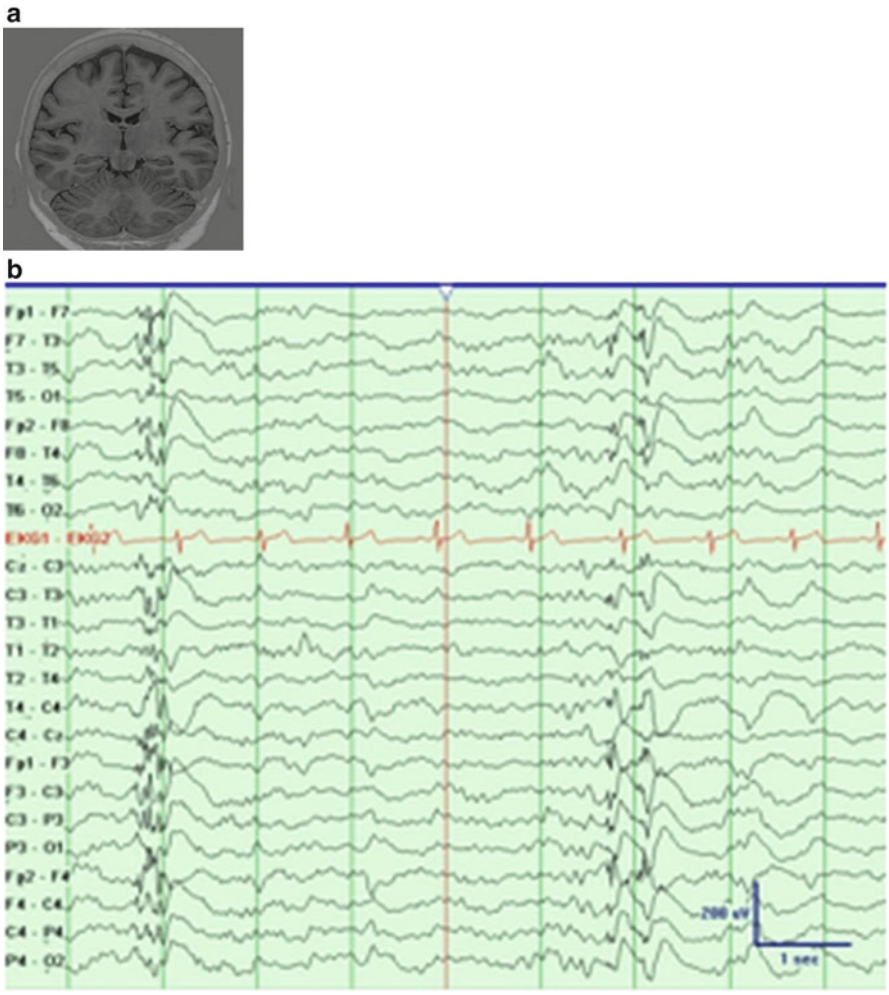

Fig. 9.1 (**a**) Normal coronal brain MRI and (**b**) EEG demonstrating a single generalized polyspike-and-wave in second 2 and generalized spike-and-waves in second 7

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.

Bibliography

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