Neurology, Psychiatry and Brain Research 27 (2018) 1–5

Contents lists available at ScienceDirect

Neurology, Psychiatry and Brain Research

journal homepage: www.elsevier.com/locate/npbr

Febrile seizure and related syndromes

José Guevara-González[a], Isabel Dimas-Rendón[a], Lucía González de Guevara[b], José Guevara-Campos[c], Omar Cauli[d,*]

[a] Pediatric Service of Hospital "Miguel Pérez Carreñ, Caracas, Venezuela
[b] Epilepsy Unit and Electroencephalography, El Tigre, Anzoátegui, Venezuela
[c] Pediatric Service of Hospital 'Felipe Guevara Rojas', El Tigre, Anzoátegui, Venezuela
[d] Department of Nursing, University of Valencia, Valencia, Spain

ARTICLE INFO

Keywords:
Febrile seizure
Epilepsy
Syndrome genetic
Febrile seizures plus
Myoclonic convulsion

ABSTRACT

Febrile seizures (FS) are the result of particular sensitivity to fever in the developing brain, have a major genetic predisposition, and nearly always have a benign outcome. Febrile seizures are the most common for of seizures in childhood. They have been observed in 2–6% of children before the age of 5 years, but in some populations this figure increase to 15%. Febrile seizures could be the first manifestations of epilepsy. About 13% of epileptic patients have a history of febrile seizures, and 30% have had recurrent febrile seizures Their phenotypic characteristics allow, in the majority of cases, a classification of the seizure, an elaboration of a prognosis and to assume a specific therapeutic attitude. It is possible to describe a spectrum according to their severity, from the benign simple seizure to the more complex, febrile seizure plus (GEFS+), Dravet syndrome, Epilepsy syndrome related infection febrile FIRES and Idiopatic Hemiconvulsion Hemiplegia and Epilepsy syndrome (IHHE). FS has a multifactorial inheritance, suggesting that both genetic and environmental factors are causative. Five areas of the genome have shown to be linked to FS in some ways. Two of them, FEB1 and FEB2 found on chromosomes 8 and 19p, are only involved in FS. During the past decade, molecular genetic studies have contributed to identification of genetic factors involved in febrile seizure and related disorders marking the necessary of careful follow up of the patients in order to detect risk factor earlier. We have reviewed the medical literature to update current knowledge of febrile seizures, their prognosis and their relation to new epileptic syndromes.

1. Introduction

Febrile seizures are the most common paroxysmal episode during childhood, affecting up to one to de 10 children. Febrile seizures (FS) are among the most common reasons that patients present with to pediatric emergencies.

FS has been recognized as a separate disease entity from other type of seizures since the early mid-nineteenth century. These seizures are classically associated with high fever in children during their lives (Hirtz et al., 2003). Their etiology and pathophysiological pathways are being understood better over time; however, there is still more to learn. Genetic predisposition is thought to be a major contributor leading to an increased susceptibility to seizure (Lennox, 1949).

Febrile seizures have been historically classified as benign; however, many emerging febrile seizure syndrome behave differently.

Lennox was the first clinician to study the background and risk factors for FS and the risk of progression to epilepsy (Lennox, 1949).

The American Academy of Pediatricś (AAP) committee of quality improvement published the first evidence-based practice parameters for FS (Baumann & Duffer, 2000). The International League Against Epilepsy (ILAE) then developed a clearer consensus regarding the recognition and treatment of children with FS (Capovilla, Mastrangelo, Romero, & Vigevano, 2009). More recently, the American Academy Pediatrics (AAP) has announced a standard definition of febrile seizures as any seizure associated with fever of > 38 °C (rectal or tympanic), but without central nervous infection (CNS), metabolic disturbance or history of afebrile seizures, in child aged 6 months to 5 years (American Academy of Pediatrics, 2008).They are the result of a particular sensitive to fever in the developing brain, have a mayor genetic predisposition, and nearly always have a being outcome.

2. Physiopatology

2.1. Epidemiology, risk factors

The life-time prevalence of one or more febrile seizures is about

* Corresponding author at: Department of Nursing, University of Valencia,Valencia, Spain.
E-mail address: Omar.Cauli@uv.es (O. Cauli).

https://doi.org/10.1016/j.npbr.2017.11.003
Received 28 September 2017; Accepted 11 November 2017

3–4% of all children in North America and western Europe, but has been reported to be somewhat higher in Finland, Japan and Guam (Annegers, Hauser, Shirts, & Kurland, 1987; Camfiel & Camfield, 2015). The peak age is 18 months with about 80% of incident febrile seizures occurring between 1 and 3 years of age (Annegers et al., 1987; Camfiel & Camfield, 2015). Several studies have explored the profile of children with a first febrile seizure (Bethune, Gordon, Dooley, Camfield, & Camfield, 1993). Factors statically associated with a febrile seizure are family history of febrile seizures, any suggestion of neurological dysfunction or developmental disability, delayed neonatal discharge, and attendance at day care (Huang et al., 1999).

Based on many studies, it becomes clear that febrile seizures have a major genetic predisposition (Camfiel & Camfield, 2015).

It has been demonstrated that there is an increased risk of febrile seizures shortly after many childhood vaccinations, including acellular pertussis (Chung, 2014; Hirtz, Nelson, & Ellenberg, 1983). It is now understood that this association is simply based on vaccine-induced fever in a susceptible child (Brown, Berkovic, & Scheffer, 2007).

Vaccine administration represents the second most common medical event associated with FS, after viral infection (Kohl et al., 2004; Principi & Esposito, 2013). Immunization has been associated with FS and an event occurring within 72 h of immunization is commonly accepted as being associated with vaccine (Kohl et al., 2004).

Exceptions are represented by the live-attenuated vaccines for which febrile seizure may be delayed until 7–14 days after vaccination. Estimates of relative risk of seizure are dependent on vaccine type and components (Brown et al., 2007). Seizure is more likely to occur after administration of certain vaccines, particularly live-attenuated vaccines such as the measles, mumps, and rubella (MMR) vaccine and toxin-2 containing or whole cell preparations such as diphtheria-tetanus-cellular pertussis (DTaP) (Blumberg et al., 1993; Braun, Montrey, Salive, Chen, & Ellenberg, 2000; Chung, 2014).

Administration of acetaminophen at the time of primary immunization with an inactive–component vaccine (DtwP-Polio) has been shown to significantly reduce or prevent the appearance of fever and found wide acceptance (Ipp et al., 1987; Lewis et al., 1988). Ibuprofen and acetaminophen have been equally recommended for administration at the time DTaP immunization, both prior to vaccination, and every 4 h for 24 h thereafter for children with a history of FS, to reduce the possibility of post-vaccination fever (Baumann & Duffer, 2000).The administration of acetaminophen and ibuprofen do not prevent febrile seizures caused by another cause. None of standard vaccinations is currently contraindicated for children with FS (Chung, 2014; Sugai, 2010).

2.2. Etiology

Febrile seizures have a familial tendency in some cases and are sporadic in others, suggesting that both genetic and environmental elements contribute to their generation (Chung, 2014). Family history also has a role in determining whether children have FS recurrences and subsequently develop afebrile seizures (Berg, Shinnar, Levy, & Testa, 1999). Twenty –five to 40% of patients showed a positive family history for FS; the incidence of FS being 20.7% among sibling, 10.9% among parents, and 14% among first degree relatives of probands (Greenberg & Holmes, 2000). Five areas of the genome have shown to be linked to FS in some way. Two of them FEB1 and FEB2, found on chromosomes 8q and 19p, are only involved in FS (Greenberg & Holmes, 2000).

A new FS susceptibility locus, FEB4 (chromosome 5q14) was suggested in nuclear FS families, indicating that FEB4 may be the most common linkage locus in FS families (Iwasaki, Nakayama, Hamano, Matsui, & Arinami, 2002). Although the mechanism of FS remains unclear, animal model are informative (Dube & Brewster Al Baram, 2009).First elevated brain temperature alters many neuronal functions, including several temperature-sensitive ion channels. Second, the fever promoting pyrogen interleukin – 1B contributes to fever generation and conversely, fever leads to the synthesis of this cytokine in the hippocampus (Shibasaki, Suzuki, Mizumo, & Tominga, 2007). In addition, intereukin – 1B has been shown to increase neuronal excitability, acting via both glutamate and GABA. These actions of interleukin 1B enhance the actions of seizure provoking agents.

Third, hyperthermia-induced hyperventilation and alkalosis have been proposed as a pivotal element of FS generation in that alkalosis of the brain provokes neuronal excitability and contributes to seizure pathophysiology (Aram & Lodge, 1987). Recently, clinicians have begun to re-classifying, febrile seizure (FS) as either simple or complex (American Academy of Pediatrics, 2008) The concept is that simple febrile seizure are associated with a very low risk of long term squeal, while complex febrile seizures carry a much greater risk (Sugai, 2010).

A simple febrile seizure last lees than < 10 min, is generalized, and does not repeat in 24 h the same illness. Subjects with simple febrile seizures have a risk of subsequent epilepsy of 2–3%, which is greater than in the general population (Camfiel & Camfield, 2015)

A complex febrile seizure may be long (> 15–20 min) is focal, or reacted in > 24 h in the same illness. Complex febrile seizures are followed by epilepsy in 4–15% (Annegers et al., 1987). One study showed a 13% incidence of epilepsy caused by the presence of at least two of the following risk factors. The risk factors for developing subsequent epilepsy after FS are summarized in Table 1.

3. Febrile status convulsive

This condition describes prolonged FS lasting more than 30 min in duration. Most of our current knowledge about this condition comes from the famous FEBSTAT study (Lewis et al., 2014). The peak age is between 12 and 24 months, and this condition is very unusual after 5 years. Two –thirds of seizures are generalized, and one-third is of focal semiology. There is no clear reason why some children tend to have prolonged FS and other does not. The Wolf-Hirschhorn syndrome (SWH) or Syndrome 4p- is a developmental disorder characterized by typical craniofacial features, delayed pre-and postnatal growth, mental retardation, severe psychomotor retardation, seizure and hypotonia. Status epilepticus occurs in half of the patients. More than 30% of children develop atypical absences from 1 to 6 years old. SWH is caused by delection in the short arm of chromosome 4 (4p16.3 region) including at least one of the genes LETM1 and WHSC1 (Motoi et al., 2016). Magnetic resonance imaging (MRI) studies show hippocampal swelling in half of patients from the third day of seizure. Whether this is the start of the process evolving into temporal lobe epilepsy has been debated for over 50 years.

4. Indications for lumbar puncture, electroencephalography, and neuroimaging studies

Recommendations by the AAP (2008) for lumbar puncture (LP) in children with first simple FS were summarized as follows: 1) in infant younger than 12 months, performance of a LP is strongly revised,

Table 1
Risk factors for developing subsequent epilepsy after FS.

Definite risk factor
Neurodevelopment abnormality
Complex FS
Family history of epilepsy
Duration of fever
Possible risk factor
> 1 complex feature
Not a risk factor
Family history of FS
Age at first FS
Peak temperature
Sex and ethnicity

because the clinical signs and symptoms associated with meningitis may be minimal or absent this age group; 2) In a child between 12 and 18 months of age, an LP should be considered, because clinical signs and symptoms of meningitis may be subtle; 3) in child older than 18 months although and LP is not routinely warranted it is recommended in the presence of meningeal signs and symptoms; 4) In infant and children who have had FS and have received prior antibiotic treatment, clinicians should be aware that treatment might mask the signs and symptoms of meningitis. These recommendations are supported in updated AAP guidelines for neurodiagnostic evaluation in children with simple FS (Febrile Seizures, 2011). As a practical consequence, LP should not be performed routinely. As started in the guidelines, current data no longer support routine LP in well-appearing fully immunized children who present with a simple FS (Chung, 2014). EEG is of limited valued in the evaluation of children with FS (Hirtz et al., 2003; Shinnar & Glauser, 2002; Subcommitee con Febriles Seizures: American Academy of Pediatrics, 2011). EEG is more likely to be abnormal in older children with FS, children with family history of FS, children with complex FS, or children with pre-existing neurodevelopment abnormalities. Although EEG abnormalities may be present in these children their clinical significance is unclear (Kanemura, Mizorogi, Aoyagi, Sugita, & Aihara, 2012). The AAP stated that EEG should not be a part of the routine evaluation in neurologically healthy children with a simple FS. However, this statement did not include patients with complex FS (5, 29, and 32). Based on evidence consensus, the AAP recommend that neuroimaging not be included in the routine evaluation of child with a first simple FS in both 1996 and 2011 (Anonymous, 1996; Hirtz et al., 2003; Subcommitee con Febriles Seizures: American Academy of Pediatrics, 2011). A recent study found MRI abnormalities in 14.8% of children with complex FS while only 11.4% of 159 children with simple FS had imagining abnormalities; however, this was not statistically significant (Hesdorffer et al., 2008). The most common abnormalities in MRI were subcortical focal hyperintensity, abnormal white matter signal, and focal cortical dysplasia.As with EEG, neuroimaging may be considered in children with neurologic abnormalities on examination and those with recurrent FS (Baumann & Duffer, 2000).

5. Treatments and prophylaxis

Approaches to the treatment of FS are based on 1) the immediate treatment of prolonged or cluster seizures. 2) Intermittent treatment at the time of illness, and 3) continuous anticonvulsant therapy for prophylaxis of FS (Patel & Vidaurre, 2013; Shinnar & Glauser, 2002).

In summary, oral/intravenous diazepam and lorazepan are the drugs of choice for aborting a prolonged seizure in an acute setting. Although antipyretics may improve the children's comfort from fever, they should not be used to prevent FS prophylactically.

Although there is evidence that both continuous antiepileptic therapy with phenobarbital and valproic acid, and intermittent therapy with oral/rectal diazepam are effective in reducing the risk of recurrence.

The AAP does not recommend that intermittent or continuous anticonvulsants be used to prevent recurrence of FS (American Academy of Pediatrics, 2008; Baumann & Duffner, 2000). A summary of the drugs and posology are shown in Table 2.

Table 2
Drugs used in febrile seizures.

Name	Dose	Route administation
Diazepan	0.5 mg/kg/dose	i.v. or oral
Lorazepan	0.1 mg/kg/dose	i.v.
Midazolan	0.03–0.1 mg/kg	i.v.
Phenobarbital	3–5 mgs/kg/day	i.v., i.m., or oral
Valproic acid route	15–50 mg/kg/day	i.v., rectal or oral
Levetiracetan	10–30 mg/kg/day	Oral route

5.1. Prognosis and outcome

Four potential adverse outcomes of FS that theoretically many be altered by an effective pharmacological agent are:

1) Decline in IQ (Intelligence quotient); 2) increased risk of epilepsy; 3) risk of recurrent FSs; and 4) death (Steering Committee on Quality Improvement & Management, 2008).

The first concern, a decline in IQ, low academic performance, neurocognitive inattention, or behavioral abnormalities, has not shown to be a consequence of recurrent simple FSs (Verity, Butler, & Golding, 1985). The second concern, increased risk of epilepsy, is more complex. Children with simple FS have approximately the same risk (1%) of developing epilepsy by the age of 7 as the general population but increased with repeated FS (Nelson & Ellenberg, 1976).

The third concern in contrast to the rare risk of developing epilepsy, is that children simple FS have a high rate recurrence. The risk varies with age. Children younger than 12 months at the time of their first simple FS have an approximately 50% probability of having recurrent FSs. Children older than 12 months at the time of their first event have an approximately 30% probability of a second FS (Berg et al., 1992). Finally, there is a theoretical risk of a child dying during a simple FS, but no case of this has yet been reported (Verity et al., 1985).

6. Epilepsy syndromes associated with fever

6.1. Gefs+

Scheffer and colleagues described several Australian families with a remarkable disorder that they initially called generalized epilepsy with seizures plus (GEFS+) (Scheffer & Berkovic, 1997).

The name has been changed to" genetic epilepsy with febrile seizures plus "(still GEFS+) because the associated epilepsy may be focal.

This disorder is typically inherited with autosomal dominance and variable penetrance. About one third of affected family members only have febrile seizures, although the febrile seizures tend to recur well beyond 5–6 years of age even up to the teenage years.

Seizures vary in their frequency, semiology, and response to treatment.

Neuroimaging is usually normal in most if not all patients. Occasionally, some patients are intellectually challenged, which leads to questioning whether the whole disorder is to be considered one of the epileptic encephalopathies (An, 2004).

About one third develop a few afebrile generalized tonic–clonic seizures in childhood with remission in adolescence. In addition, some families include patients with focal epilepsy, particularly temporal lobe epilepsy, of varying severity. A rare member of a GEFS+ kindred may develop Dravet syndrome, although most Dravet patient have de novo SCN1A mutations and are not members of GEFS + families (De jonghe, 2011).Genetic studies of GEFS+ families have found that many, but not all, have a mutation in SCN1A, typically a misses mutation. Currently most experts in molecular genetics classify GEFS+ into three groups based on the underlying genetic makeup. GEFS+ type 1 is usually linked to SCN1B gene mutation, GEFS+ type 2 to SCN1A, and GEFS+ type 3 to GABRG 2 gene mutation (Incorpora, Pavone, & Ruggieri, 2012).

The latter is the only gene that encodes sodium channels. The most mysterious among those genes is the SCN1A beta subunit, which is located in 2q24.3 and linked to GEFS+ type 2. This sodium channel-encoding gene has been linked to many neurological syndromes of variable clinical spectra and severity. Examples of theses syndromes include early infant epileptic encephalopathy (Ohtahara Syndrome) severe myoclonic epilepsy of Infancy (Dravet syndrome) myoclonic astatic epilepsy (Doose syndrome) and familial hemiplegic migraine type 3 (Lim, Hwang, & Kim, 2015).

The clinical utility of SCN1A genetic testing for GEFS+ is limited because few families (approximately 10%) have been found to have

genetic mutations, and the identification of a mutation does not predict the phenotype that will develop in an individual (Shinichi, Ingrid, Carla, Peter, & Eva, 2013).

6.2. Dravet syndrome

Dravet syndrome (DS) typically presents around 6 months of age, are previously well children, with prolonged, febrile and afebrile, generalized or hemiclonic epileptic seizures. Other seizures types including myoclonic, focal and atypical absence seizures appear between the age of 1 and 4 years (Dravet, Bureau, & Oguni, 2005)

The epilepsy is usually not responsive to standard antiepileptic medication, and affected children develop cognitive, behavioral, and motor impairment (Nabbout, Chemaly, & Chipaux, 2013a).

Seizures are often associated with fever or occur shortly after vaccinations, which had led so the misdiagnosis of vaccine encephalopathy, focal and atypical absence seizures may begin between 1 and 4 years. Infants with DS usually develop normally in the first year. Suspected Dravet syndrome (DS) is the principal indication for SCN1A testing and 70–80% of cases have a demonstrable mutation (Shinichi et al., 2013).

6.3. Fires

FIRES are characterized by development of seizures in healthy children during or a few days following nonspecific febrile infection (Van Baalen, Stephani, & Kluger, 2009). Seizures rapidly aggravate and turn to status epilepticus followed by pharmacoresistant epilepsy and cognitive function deficit.

This syndrome constitutes another emerging disease entity that is closely related to FS and epilepsy. In their multicenter study on 77 patients with FIRES, Kremer et al., estimated its prevalence to be 1:100.000 children, but many think this number might be an underestimate (Kramer, Chi, & Lin, 2011). The etiology of this syndrome is not exactly known; the proposed inflammatory and immunological factors have not been confirmed yet. Most patients are between 3 and 15 years old and boys are affected more than girls (Kramer et al., 2011).

Most seizures are focal at the beginning, but an evolution to generalize seizures is common. Many patients develop a number of neurological symptoms over time, including learning and motor difficulties behavioral changes, nonspecific sensory symptoms, and memory deficit (Caraballo, Reyes, & Avaria, 2013). The EEG between seizures shows slow waves over the whole brain that neurophysiologist tends to quality as an 'encephalitis' pattern. Others EEG studies often show generalized slow background with ictal frontal and temporal epileptiform activity. Brain imagining studies are initially normal but over time demonstrate progressive brain atrophy with or without temporal hyperintensities (Nabbout, Mazzuca, & Hubert, 2010).

Antiepileptic medications are often ineffective. The role of immunotherapy is questionable, though Sakuma et al. have report a success rate of 85% with steroid. In their study, however, was no response to intravenous immunoglobulins (IVIG) (Sakuma et al., 2010). One possible promising treatment option is the ketogenic diet, which has been reported to have some success in a few case reports (Nabbout et al., 2010).

The syndrome is occasionally fatal, and the overall prognosis is poor, but most patients are ambulant with mild to moderate intellectual disturbance.

6.4. IHHE

IHHE is characterized by combination of unilateral convulsive status epilepctus (SE), mainly clonic, followed by transient or permanent ipsilateral hemiplegia. It occurs in infants during the course of a nonspecific febrile illness, mainly in the first 2 years of life and in any case before the age of 4 years (Gastaut et al., 1960).

SE is usually long and might persist for hours if not treated. HHE was reported as "symptomatic" in many instances, since it complicates the course of preexisting brain disorder, that is, Sturge Weber disease, and agenesis of the corpus callosum or tuberous sclerosis. However, many cases are idiopathic IHHE and occur in apparently healthy infant who exhibit neither clinical nor imaging evidence of preexisting brain lesion.

Seizures start with rhythmic unilateral, they predominate on one side and last several hours, up to 24 h. Ictal electroencephalography (EEG) shows high amplitude fast activity and rhythmic spikes contralateral to the predominating jerks (Chauvel & Dravet, 2005).

It has been proposed that HHE syndrome,along with fever –induced refractory epileptic encephalopathy in school-aged children (FIRES) and new –onset refractory status epilepticus (NORSE),may be part of the same spectrum of inflammatory mediated encephalopathy and status epilepticus syndromes with the difference in clinical expression related to the stage of brain maturation. Recent report has linked it with CACNA1A mutation and possible cerebral vasospasm (Nabbout, Vezzani, & Dulac, 2011).

Magnetic resonance imaging (MRI) shows increased diffusion on one side, mainly in the perisylvian and parietooccipital areas, followed by atrophy (Nabbout, et al., 2013). The febrile status epilepticus has decreased with the use of benzodiazepines as rescue therapy in long –lasting febrile seizures.

7. Conclusions

Although febrile seizures are commonly benign, most families consider them very frightening. It is important to realize some special febrile seizure syndromes, which can have some long-term neurological abnormalities. More studies are still needed to help the medical community's understanding of the mechanisms, pathways, correlations, and clinical implications of FS and FS-related syndromes.

Conflict of interest

Author declare no conflict of interest.

References

American Academy of Pediatrics (2008). Steering Committee on Quality Improvement and Management, Subcommittee on Febrile Seizures: Clinical practice guideline for long term management of child with simple febrile seizures. *Pediatrics, 121*, 1281–1286.

An, Gourfinkel I. (2004). Generalized epilepsy with febrile seizure-plus syndrome. *Orphanet Encyclopedia* Available at: https://www.orpha.net/data/patho/GB/uk-GEFS.pdf.

Practice parameter the neurodiagnostic evaluation of the child with a first simple febrile seizure. American Academy of Pediatrics. Provisional Committee on Quality Improvement. Subcommitee on febrile seizures Pediatrics 1996; 97: 769–772.

Annegers, J. F., Hauser, W. A., Shirts, S. B., & Kurland, L. T. (1987). Factors prognostic of unprovoked seizures after febrile convulsion. *The New England Journal of Medicine, 316*, 494–498.

Aram, J. A., & Lodge, D. (1987). Epileptiform activity induced by alkalosids in rat neocortical slices: Block by antagonist of *N*-methyl-D-aspartate. *Neuroscience Letters,* 345–350.

Baumann, R. J., & Duffer, O. K. (2000). Treatment of children with simple febrile seizures: The AAP practice parameter. *Pediatric Neurology, 23*, 11–17.

Baumann, R. J., & Duffner, P. K. (2000). Teatment of children with simple seizures: The AAP practice parameter. *American Academy of Pediatrics Pediatrics Neurology, 2* [23-11-7].

Berg, A. T., Shinnar, S., Hauser, W. A., Alemany, M., Shapiro, E. D., Salomon, M. E., et al. (1992). A prospective study of recurrent febrile seizures. *The New England Journal of Medicine, 327*, 1122–1127.

Berg, A. T., Shinnar, S., Levy, S. R., & Testa, F. M. (1999). Childhood-onset epilepsy with and without preceding febrile seizures. *Neurology, 53*, 17–42.

Bethune, P., Gordon, K. G., Dooley, J. M., Camfield, C. S., & Camfield, P. R. (1993). Which child will have a febrile seizure? *American Journal of Diseases of Children, 147*, 129–134.

Blumberg, D. A., Lewia, K., Mink, C. M., Christenson, P. D., Chatfield, P., & Cherry, J. D. (1993). Severe reactions associated with diphtheria-tetanus-pertussis vaccine: Detailed study of children with seizures hypotonic-hyporesponsive episodes, high fevers, and persistent crying. *Pediatrics, 91*, 1158–1165.

Braun, M. M., Montrey, G. T., Salive, M. E., Chen, R. T., & Ellenberg, S. S. (2000). Infant immunization with acelular pertussis vaccines in the United States; assessment of the first two years data from the Vaccine Advers Event Reoorting System (VAERS). *Pediatrics, 106*, E51.

Brown, N. J., Berkovic, S. F., & Scheffer, I. E. (2007). Vaccination, seizures and vaccine damage. *Current Opinion in Neurology, 20*, 181–187.

Camfiel, P., & Camfield, C. (2015). Febrile seizures and genetic epilepsy with febrile seizure plus (GEFS+). *Epileptic Disorders, 17*, 124–132.

Capovilla, G., Mastrangelo, M., Romero, A., & Vigevano, F. (2009). Recommendations for the management of febrile seizures: Ad Hoc task of LICE guidelines commission. *Epilepsia, 50*, 2–6.

Caraballo, R. H., Reyes, G., Avaria, M. E. L., et al. (2013). Febrile infection –related epilepsy syndrome a study of 12 patients. *Seizure, 22*(7), 553–559.

Chauvel, P., & Dravet, C. (2005). The HHE syndrome. In J. Roger, M. Bureau, C. Dravet, P. Genton, C. Tassanari, & P. Wolf (Eds.). *Epileptic syndrome in infancy childhood and adolescence* (pp. 247–260). Paris: 4th and John Libbey.

Chung, S. (2014). Febrile seizures. *The Journal of Pediatrics, 57*(9), 384–395.

De jonghe, P. (2011). Molecula genetics of Dravet syndrome. *Developmental Medicine & Child Neurology, 53*(2), 7–10.

Dravet, C., Bureau, M., Oguni, H., et al. (2005). Severe myoclonic epilepsy in infancy (Dravet syndrome). In J. Roger, M. Bureau, C. Dravet, P. Genton, C. A. Tassainari, & P. Wolf (Eds.). *Epileptic syndromes in infancy childhood and adolescence* (pp. 89–113). London: John Libbey.

Dube, C. M., & Brewster Al Baram, T. Z. (2009). Febrile seizures: Mechanisms and relationship to epilepsy. *Brain and Development, 31*, 366–371.

Febrile Seizures (2011). Guideline for the Neurodiagnostic Evaluation of the Child With a simple febrile seizure. *Pediatrics, 127*, 389–394.

Gastaut, H., Poirier, F., Payan, H., Salomon, G., Toga, M., & Viigouroux, M. (1960). HHE syndrome; hemiconvulsion, hemiplegia, epilepsy. *Epilepsia, 1*, 418–447.

Greenberg, D. A., & Holmes, G. L. (2000). The genectics of febrile seizures. In T. Z. Baran, & S. Shinnar (Eds.). *Febrile seizures* (pp. 249–261). San Diego: Academic Press.

Hesdorffer, D. C., Chan, S., Tian, H., Allen Hauser, W., Dayan, P., Leary, L. D., et al. (2008). Are MRI–detected brain abnormalities associated with febrile seizure type? *Epilepsia, 49*, 765–771.

Hirtz, D. G., Nelson, K. B., & Ellenberg, J. H. (1983). Seizures following childhood immunizations. *The Journal of Pediatrics, 120*, 14–18.

Hirtz, D., Berg, A., Bettis, D., Camfield, C., Camfield, P., Crumrine, P., Gaillard, W. D., Schneider, S., Shinnar, S., Quality Standards Subcommittee of the American Academy of Neurology, & Practice Committee of the Child Neurology Society (2003). Practice parameter: treatment of the child with a first unprovoked seizure: Report of the Quality Standards Subcommittee of the American Academy of Neurology and the Practice Committee of the Child Neurology Society. *Neurology, 60*(2), 166–175.

Huang, C. C., Wang, S. T., Chang, Y. C., Huang, M. C., Chi, Y. C., & Tsai, J. J. (1999). Risk factors for a first febrile convulsion in children a populations study in Southern Taiwan. *Epilepsia, 40*, 719–725.

Incorpora, G., Pavone, P., Ruggieri, M., et al. (2012). Generalized epilepsy with febrile seizures plus (GEFS+): Molecular analysis in a restricted area. *Childs Nervous System, 28*, 141–145.

Ipp, M. M., Gold, R., Greenberg, S., Goldbach, M., Kupfert, B. B., Lloyd, D. D., et al. (1987). Acetaminophen prophylaxis of adverse reactions following vaccination of infants with diphtheria-pertussis-tetanus toxoids polio vaccine. *The Pediatric Infectious Disease Journal, 6*, 721–725.

Iwasaki, N., Nakayama, J., Hamano, K., Matsui, A., & Arinami, T. (2002). Molecular genetics of febrile seizures. *Epilepsia, 43*(Suppl. 9), 32–35.

Kanemura, H., Mizorogi, S., Aoyagi, K., Sugita, K., & Aihara, M. (2012). EEG characteristics predict subsequent epilepsy in children with febrile seizure. *Brain and Development, 34*, 302–307.

Kohl, K. S., Marcy, S. M., Blum, M., Connell Junes, M., Dagan, R., Hansen, J., et al. (2004). Fever after immunization: Current concepts and improved future scientific understanding. *Clinical Infectious Diseases, 39*, 389–394.

Kramer, U., Chi, S., Lin, K. L., et al. (2011). Febrile infection-related epilepsy syndrome (FIRES) pathogenesis, treatment, and outcome a multicenter study on 77 children. *Epilepsia, 52*(11), 1956–1965.

Lennox, M. A. (1949). Febrile convulsion in childhood, a clinical and electroencephalographic study. *American Journal of Diseases of Children, 78*, 868–882.

Lewis, K., Cherry, J. D., Sachs, M. H., Woo, D. B., Hamilton, R. C., Tarle, J. M., et al. (1988). The effect of prophylactic acetaminophen administration on reactions to DTP vaccination. *American Journal of Diseases of Children, 42*, 62–65.

Lewis, D. V., Shinnar, S., Hesdorffer, D. C., Bagiella, E., Bello, J. A., Chan, S., Xu, Y., MacFall, J., Gomes, W. A., Moshé, S. L., Mathern, G. W., Pellock, J. M., Nordli, D. R., Jr, Frank, L. M., Provenzale, J., Shinnar, R. C., Epstein, L. G., Masur, D., Litherland, C., Sun, S., & FEBSTAT Study Team (2014). Hippocampal sclerosis after febrile status epilepticus: the FEBSTAT study. *Annals of Neurology, 75*(2), 178–185.

Lim, B. C., Hwang, H., Kim, H., et al. (2015). Epilepsy phenotype associated with a chromosome 2q24. 3 deletion involving SCNIA: Migrating partial seizures of infancy or atypical dravet syndrome. *Epilepsy Research, 109*, 29–34.

Motoi, H., Okanishi, T., Kanai, S., Yokota, T., Yamazoe, T., Nishimura, M., Fujimoto, A., Yamamoto, T., & Enoki, H. (2016). Wolf-Hirschhorn (4p-) syndrome with West syndrome. *Epilepsy & Behavior Case Reports, 15*(6), 39–41.

Nabbout, R., Mazzuca, M., Hubert, P., et al. (2010). Efficacy of ketogenic diet in severe refractory status epilepticus initiating fever induced refractory epileptic encephalopathy in school age children (FIRES). *Epilepsia, 51*(10), 2033–2037.

Nabbout, R., Vezzani, A., Dulac, O., et al. (2011). Acute encephalopathy with inflammation- mediated status epilepticus. *Lancet Neurology, 10*, 99–108.

Nabbout, R., Chemaly, N., Chipaux, M., et al. (2013). Encephalopathy in children with Dravet syndrome is not a pure consequence of epilepsy. *Orphanet Journal of Rare Diseases, 8*, 176.

Nabbout, R., FIRES, & IHHE (2013). Delineation of the syndromes. *Epilepsia, 54*(6), 54–56.

Nelson, K. B., & Ellenberg, J. H. (1976). Predictors of epilepsy in children who have experienced febrile seizures. *The New England Journal of Medicine, 295*, 1029–1033.

Patel, A. D., & Vidaurre, J. (2013). Complex febrile seizures a practical guide to evaluation and treatment. *Journal of Child Neurology, 28*, 762–767.

Principi, N., & Esposito, S. (2013). Vaccines and febriles seizures. *Expert Review of Vaccines, 12*, 885–892.

Sakuma, H., Awaya, Y., Shiomi, M., Yamanouchi, H., Takahashi, Y., Saito, Y., Sugai, K., & Sasaki, M. (2010). Acute encephalitis with refractory, repetitive partial seizures (AERRPS): a peculiar form of childhood encephalitis. *Acta Neurologica Scandinavica, 121*(4), 251–256.

Scheffer, I. E., & Berkovic, S. F. (1997). Generalized epilepsy with febrile seizures+: A genetic disorder with heterogeneous clinical phenotypes. *Brain, 120*, 479–490.

Shibasaki, K., Suzuki, M., Mizumo, A., & Tominga, M. (2007). Effects of body temperature on neural activity in the hippocampus: Regulations of resting membrane potentials by transient receptor potencial vanilloid 4. *The Journal of Neuroscience, 27*, 1566–1575.

Shinichi, H., Ingrid, E., Scheffer, Carla, M., Peter, D. J., Eva, A., et al. (2013). SCNIA testing for epilepsy: Application in clinical practice. *Epilepsia, 54*(5), 946–952.

Shinnar, S., & Glauser, T. A. (2002). Febrile seizures. *Journal of Child Neurology, 17*(Suppl. 1), S44–S52.

Steering Committee on Quality Improvement and Management (2008). Subcommittee on Febrile seizures American Academy of Pediatrics. Febrile seizure: Clinical practice guideline for the long-term management of the child with simple febrile seizures. *Pediatric, 121*, 1281–1286.

Subcommitee con Febriles Seizures: American Academy of Pediatrics (2011). Neurodignostic evaluation of child with a simple febrile seizure. *Pediatrics, 127*, 389–394.

Sugai, K. (2010). Currrent management of febrile seizures in Japan: An overview. *Brain and Development, 32*, 64–70.

Van Baalen, A., Stephani, U., Kluger, G., et al. (2009). FIRES: Febrile infection responsive epileptic (FIRE) encephalopathies of school age. *Brain and Development, 31*, 92–93.

Verity, C. M., Butler, N. R., & Golding, J. (1985). Febrile convulsions in a national cohort followed up from birth. II—Medical history and intellectual ability at 5 years of age. *British Medical Journal (Clinical Research Edition), 290*, 1311–1315.