Febrile seizures

From molecular biology to clinical practice

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ABSTRACT

Febrile seizures occur between the age of 3 months and 5 years with a temperature of 38°C or higher, and are either simple or complex. Eight gene loci have been identified to be associated with certain cases of autosomal dominant familial febrile seizures, and 12 genes have been associated with some of the familial epilepsy syndromes that can start with febrile seizures. The mutations and the protein products are known for only some of these 20 genes. The risk of recurrence of convulsions in a further febrile illness is on average 30%, and of developing epilepsy is on average 6%, but both vary depending on the presence and number of risk factors in any given patient. The immediate treatment of a febrile convulsion is intravenous or rectal diazepam, but febrile status epilepticus requires intravenous Phenobarbital and possibly other medications. Long-term antiepileptic drugs are not recommended in most patients with febrile seizures. However, exceptions should be considered on an individual basis in patients with complex febrile seizures with multiple risk factors for development of later epilepsy.

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Febrile seizures are seizures that occur between the age of 3 months and 5 years with a temperature of 38°C or higher and are not the result of central nervous system infection or any metabolic imbalance. They are either simple (referred to as typical) or complex (atypical): 1. A simple febrile seizure is a primary generalized, usually tonic-clonic attack, associated with fever, lasting for a maximum of 15 minutes, not recurring within a 24-hour period. 2. Complex febrile seizures, however, are more prolonged (more than 15 minutes), focal or recur within 24 hours, or both.[1] Between 2-5% of neurologically healthy infants and children experience at least one, usually simple, febrile seizure.

Clinical course and long-term prognosis. The risk of recurrence. Recurrence of febrile seizures occurs in 30% of those experiencing a first episode, in 50% after 2 or more episodes, and in 50% of infants less than one year of age.[1] Several factors affect this recurrence risk (**Table 1**). In the Berg and colleagues series,[2,3] 347 children with a first febrile seizure were followed up for an average of 20 months. The predictors of recurrence were short duration of illness before the seizure, low body temperature at the time of seizure, a family history of febrile seizures, and age at first seizure less than 18 months. Knudsen[4] reported 6 'additive' predictive factors for recurrence: complex nature of the febrile seizure, age less than 14 months, family history of febrile seizures, family history of epilepsy, attendance at day care, and developmental delay. The risk for an individual child ranged from 12% if none of these factors were present to 100% if all were present. Risk factors for febrile seizure recurrence in the study by Bessisso and colleagues[5]

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Table 1 - Predictors of recurrence of febrile seizures.

Risk factor	References
Age at 1st seizure	
<18 months	Berg et al[2]
<14 months	Knudsen,[4] Nelson & Ellenberg[75]
Low body temperature at time of seizure	Berg et al,[2] El Radhi et al[6]
Positive family history of febrile seizures	Berg et al,[2] Knudsen[4]
Positive family history of epilepsy	Knudsen,[4] Rich et al22
Complex nature of febrile seizure	Knudsen,[4] Bessisso et al[5]
Short duration of illness/ fever before seizure	Berg et al[2]
Attendance at day care	Knudsen[4]
Low serum sodium levels	Hugen et al[7]
Male sex	Bessisso et al[5]

were male sex and having complex febrile seizures. El-Radhi[6] studied 132 children with their first febrile seizure, measured their body temperature at the onset of the seizure, and followed them for an average of 2 years. Children whose body temperature was 39°C, at the onset of the seizure, were 2.5 times more likely to have multiple convulsions within the same illness (when their temperature rose above that which caused the initial convulsion) than those with a temperature less than 39°C. These patients were also 3 times more likely to experience recurrent febrile convulsions in subsequent illnesses. Hugen and colleagues[7] found an almost linear association between serum sodium levels and recurrent febrile convulsions - the lower the level, the higher the risk.

The risk of brain damage. There are no long-term adverse effects of having one or more simple febrile seizures. Specifically, recurrent simple febrile seizures do not damage the brain. Several hospital-based studies have reported deficits in speech, drawing, arithmetic, attention and intelligence in patients with febrile seizures. However, these series are considered biased (due to referral patterns) and such findings have not been confirmed by other controlled and population based studies. The study of Kolfen et al (1998)[8] compared 80 children 6-9 years old, with a history of febrile convulsions, with matched healthy controls. Of note is that the group with febrile seizures included children with prolonged febrile convulsions (18%) and some children with discrete neurological abnormalities (7%). Neuropsychological test results were no different between children with febrile seizures and their healthy controls. However, in children with prolonged febrile convulsions nonverbal intelligence was found to be significantly lower as compared to children with simple febrile seizures and with controls. The population-based study in the United Kingdom, comprehensively assessed 381 children with febrile convulsions (simple or complex) at 10 years of age and compared them with healthy children using measures of academic progress, intelligence, and behavior - there was no difference.[9] A recent case-control population based study was conducted on 103 children with confirmed febrile seizures by 3 years and followed up until age 6 years. Compared with age-matched controls, there were no adverse effects on behavior, scholastic performance or neurocognitive attention.[10,11]

The risk of developing epilepsy. Although approximately 15% of children with epilepsy have had febrile seizures,[12] only 2-7% of children who experience febrile convulsions proceed to develop nonfebrile seizure disorders and epilepsy later in life.[13] There are several predictors of epilepsy after febrile seizures. Complex febrile seizures, neurodevelopmental abnormalities, a family history of epilepsy, recurrent febrile seizures, and a brief duration of fever before the initial febrile seizure were all associated with an increased risk of epilepsy in the study by Berg and Shinnar (1996).[14] However, in other studies multiple recurrences did not predict subsequent epilepsy.[12,15] Verity and Golding in 1991[16] demonstrated that a higher risk for later epilepsy occurs in patients with complex febrile seizures (6%) particularly focal febrile seizures (29%), as compared to simple febrile seizures (1%). Febrile seizures, often, precede generalized afebrile tonic-clonic seizures. Prolonged febrile seizures, can also, precede intractable complex partial seizures.[12] Choueiri et al (2001)[17] showed that 36% of patients with temporal lobe epilepsy (TLE) had prior febrile seizures, and that only 6% of patients with primary generalized epilepsy had such a history. It is possible that some patients who develop febrile status epilepticus develop neuronal injury and secondary epilepsy, often secondary to medial temporal sclerosis. Despite that, the earlier mentioned increased risk for later epilepsy after febrile seizure is thought to be predominantly due to genetic predisposition and probably only to a lower extent due to structural damage to the nervous system caused by recurrent febrile seizures. However, this issue is not yet fully resolved.

Genetic factors. The genetic component for febrile seizures is manifested by its positive relation with family history of febrile and afebrile seizures documented in several studies.[13,17-21] The study by Choueiri et al (2001)[17] showed that patients with febrile seizures were more likely to have a family history of febrile seizures (20%) than patients with epilepsy (1.1%). They did not have an increased

frequency of consanguinity which favored an autosomal dominant rather than recessive inheritance. Rich et al (1987)[22] performed complex segregation analysis on 467 nuclear families ascertained through probands with febrile convulsions. Nearly dominant seizure susceptibility was found in families of probands with multiple febrile convulsions while families of probands with single febrile convulsions followed the polygenic model of inheritance. A systematic pedigree study of 52 probands was conducted by Johnson et al (1996).[23] Polygenic inheritance was found in some smaller families and there was no evidence of X-linked or mitochondrial inheritance. Penetrance was calculated to be 0.64 representing an estimate of the upper limit of penetrance and in agreement with twin studies. In a study in India by Wadhwa et al (1992),[21] out of 144 cases of febrile seizures (95 simple and 49 complex), 20% had familial prevalence of febrile seizures (same percentage in both groups). However, 13.9% had family history of afebrile seizures (13.2% in the simple and 40.8% in the complex group). Similarly, it has been documented that the familial type of febrile seizures is not necessarily associated with the initial febrile seizure being complex in nature.[20] Four febrile convulsions gene loci with autosomal dominant inheritance have been identified in patients with febrile seizures. These include FEB1 on 8q13-q21 in an Australian family,[24] FEB2 on 19p in an American family,[13] and FEB3 on 2q23-q24.[25] Other investigators have mapped genetic loci responsible for generalized epilepsy with febrile seizures plus (GEFS+) to 2q21-q33, 2q24-q33, and 2q23-31 overlapping with FEB3.[26-28] However, in the above FEB3 family, described by Peiffer et al,[25] the phenotypic manifestations differed from that of GEFS+ in that these patients only had febrile seizures without the other seizure types of GEFS+.[25] More recently, Nakayama et al (2000)[18] identified a new gene on 5q14-q15 that gives susceptibility to febrile seizures discovered in Japanese families, which they called FEB4. Other febrile convulsion gene loci were identified and are shown in **Table 2**.

Table 2 - Identified gene loci of febrile seizures.

Gene locus*	References
FEB1 on 8q13-21	Wallace et al[24] (Australian)
FEB2 on 19p13.3	Johnson et al[13] (American)
FEB3 on 2q23-q24†	Peiffer et al[25] (American)
FEB4 on 5q14-q15	Nakayama et al[18] (Japanese)
On 6q22-q24	Nabbout et al[76] (French)
Nonsense mutation S2652X (MASS1 gene)	Nakayama et al[77] (Japanese)
(Ser543Ser)-C/T (CHRN4 gene)	Chou et al[78] (Chinese)
R43Q mutation on chromosome 5 (GABA(A) receptor γ2-subunit gene, GABRG2)**	Marini et al[79] (Australian)

*All autosomal dominant inheritance
†Other investigators have mapped gene loci for GEFS+ syndrome to 2q21-q33, 2q24-q33, and 22q23-31 overlapping with FEB3, however the phenotype described by Peiffer et al differed from GEFS+.
**Other investigators have identified mutations for GEFS+ and Dravet Syndrome in the GABA(A) receptor γ2-subunit, however this mutation affects a different domain of the subunit.
GEFS+ - generalized epilepsy with febrile seizures plus
GABA - gamma-aminobutyric acid

Several genetic epilepsy syndromes can start with febrile seizures. These are GEFS+, severe myoclonic epilepsy in infancy (SMEI or Dravet's syndrome), and TLE. The GEFS+ is an autosomal dominant syndrome with a highly variable phenotype. Onset is usually in early childhood and remission is usually in mid childhood. It is characterized by multiple febrile seizures, and several types of afebrile generalized seizures including generalized tonic clonic, absence, myoclonic or atonic and myoclonic astatic seizures with variable degrees of severity.[29,30] One type is GEFS+1 which has been linked to mutations in the gene SCN1B on 19q13 encoding the β1 subunit of the voltage-gated sodium channel.[31] The probable mechanism of seizure onset is that the mutation on SCN1B (19q13) disrupts a disulfide bond that maintains the extra-cellular fold motif of the β1 subunit. Such disruption results in slower inactivation of the sodium (Na) channel and, thus, in increased excitability. Temperature sensitivity may reflect the effects of temperature on conductance and gating of Na channels. Another type (GEFS+2) has shown linkage to 2q21-q33 locus in a family studied by Baulac et al (1999),[26] and to 2q24-q33 locus in the family reported by Moulard et al (1999).[27] Escayg et al (2000)[32] later demonstrated that the above mutations were linked to gene SCN1A encoding for the alpha subunit of the voltage-gated sodium channel.[32] In addition, Lopes-Cendes et al (2000)[28] identified a new locus for GEFS+2 on 2q23-q31. A K289M mutation in the gamma-aminobutyric acid (GABA) (A) receptor gamma2-subunit gene has been reported in a family with GEFS+ phenotype and was identified as the GEFS+3 type.[33]

Severe myoclonic epilepsy of infancy (SMEI) or Dravet's syndrome is considered to be the most severe of the phenotypic spectrum of febrile seizures plus. It constitutes a distinctive separate entity which is one of the most severe forms of epilepsy in infancy.[34] Its onset is in the 1st year of life, characterized by febrile and afebrile unilateral clonic seizures recurring monthly or every 2

months. These early seizures are typically induced by fever, but they differ from the usual febrile convulsions in that they are more prolonged, more frequent, and come in clusters. Seizures subsequently start to occur with lower fevers and then without fever. During the 2nd year of life, myoclonus, atypical absences, and partial seizures occur frequently and developmental delay usually follows. A family history of epilepsy was found in 25-30% of patients, suggesting a genetic etiology.[35] This syndrome has been shown to have autosomal dominant or sporadic inheritance. The mutated gene is located on 2q24-31 and encodes for SCN1A, the same gene mutated in GEFS+ spectrum. However, studies have correlated it to de novo truncation mutations, whereas in GEFS+ they are missense mutations.[36,37] In the study by Claes et al (2001),[36] all 4 patients with SMEI had mutations in the alpha subunit of the neuronal voltage-gated sodium channel SCN1A located on chromosome 2q.[36] Sugawara et al (2002)[37] screened 12 patients with SMEI and found 10 mutations all of which lead to the truncation of the protein. Harkin et al (2002)[38] studied an Australian family with GEFS+ having one member with SMEI. The SMEI phenotype was shown to be resulting from a mutation in the γ-2 subunit of the GABA(A) receptors.

Febrile seizures have been reported to occur in patients with familial TLE. In 1993, Abu Khalil et al[39] reported 47 patients with TLE who underwent surgery. Nineteen of these patients (40%) have had febrile convulsions preceding the onset of their afebrile seizures and were more likely to have a positive family history of febrile seizures (59 versus 18%) suggesting a genetic factor.[39] The familial TLE described by Berkovic et al (1996)[40] has its onset in adolescence with no preceding febrile seizures but with simple partial seizures with psychic and cognitive features and only a low frequency of febrile seizures in family members (2.7%). In the familial cases of mesial TLE with hippocampal atrophy described by Kobayashi et al (2001),[41] the incidence of febrile seizures in patients was slightly more (6%), and 84% had simple partial seizures consisting of autonomic signs and symptoms. In a third, French, family with TLE with febrile seizures, Baulac et al (2001),[42] identified another form of familial TLE without hippocampal sclerosis, with 100% of the patients initially experiencing simple febrile seizures and subsequently developing afebrile (mainly partial) seizures at approximately age 9 years. Gene loci identified in the above family were on chromosomes 18qter and 1q25-31. Recently, Depondt et al (2002)[43] described a fourth distinct autosomal dominant TLE syndrome in a large Belgian family with high incidence of febrile seizures among family members (50%). Six of the 10 patients with TLE had preceding febrile seizures, and none had hippocampal sclerosis. Age of onset of afebrile seizures ranged from 10 months to 34 years. The study found no evidence for linkage to any of 13 candidate loci for familial partial seizures and febrile seizures.[43] There are also other genetic epilepsy syndromes which were found to be associated with febrile seizures (included in **Table 3**).

Workup of a child with febrile seizures. Each child that presents with a febrile seizure deserves a thorough, detailed history and general and neurological examinations. These are the corner stone of the evaluation. Several investigations need to be considered.

Lumbar puncture. Lumbar puncture is recommended in children younger than 12 months of age after their first febrile seizure to rule out meningitis and is especially important to consider if the child has received prior antibiotics that would mask the clinical symptoms of the disease. Moreover, the presence of an identified source of fever like otitis media does not eliminate meningitis. Seizures are the major signs of meningitis in 13-15% of presenting children of which 30-35% have no other meningeal signs. According to the American Academy of Pediatrics (AAP) practice parameter, it is strongly recommended in infants less than one year of age, as signs of the infection might not even be present. A child between 12 and 18 months should also be considered for lumbar puncture as there are usually slight symptoms of meningitis clinically. For children above 18 months, a lumbar puncture is needed in the presence of clinical signs and symptoms of meningitis (such as neck stiffness, Kernig and Brudzinski signs) or if the case suggests intracranial infection.[44]

EEG. If the child is presenting with his first simple febrile seizure, and is otherwise, healthy (neurologically), an EEG should not normally be performed as part of his evaluation.[45] According to Alvarez et al (1983)[46] and Doose et al (1983),[47] hypnagogic spike waves are seen in children with febrile seizures particularly those over 4 years old. However, the performance of an EEG would not predict the future recurrence of febrile seizures or epilepsy even if the result is abnormal. If an EEG is carried out, it should be performed for at least half an hour in wakefulness and in sleep according to international guidelines to avoid misinterpretations and erroneous conclusions. An EEG performed within 2 weeks of a febrile seizure will often have more specific usually posterior slowing. Thus, frequently, the EEG is delayed until after 2 weeks have passed, or if carried out during that period it needs to be repeated. Because of all the above reasons, performance of an EEG should be highly restricted to special cases in whom epilepsy is highly suspected only.

Blood studies. The following blood studies are not routinely recommended in the workup of a child

Table 3 - Genetic epilepsies that often start with febrile seizures.

Syndrome	Type	Gene locus	Gene product	Inheritance	Reference(s)
GEFS+	GEFS+1 (Australian)	19q13 (SCN1B)	β1 subunit of the voltage-gated sodium channel	AD	Wallace[31]
	GEFS+2	2q21-q33 (SCN1A, SCN2A)	α subunit of the voltage-gated sodium channel	AD	Baulac,[26] Escayg,[32] Sugawara[80]
		2q24-q33 (SCN1A, SCN2A)	α subunit of the voltage-gated sodium channel	AD	Moulard,[27] Escayg,[32] Sugawara[80]
		2q23-q31 (SCN1A, SCN2A)	α subunit of the voltage-gated sodium channel	AD	Lopes-Cendez,[28] Escayg,[32] Sugawara[80]
	GEFS+3 (French)	5q31.1-q33.1 (GABRG2 gene)	GABA(A) receptor γ2-subunit	AD	Baulac[33]
Severe myoclonic epilepsy of infancy (Dravet Syndrome)	(Belgian)	2q 24-q31 (SCN1A, SCN2A)	α subunit of the voltage-gated sodium channel	AD	Claes,[36] Sugawara[80]
	(Australian)	(GABRG2)	GABA(A) receptor γ2-subunit	AD	Harkin[38]
Familial Temporal Lobe Epilepsy	(AngloSaxon, Italian)	Not identified (chr 3, 6, or 15)	–	AD	Berkovic[40]
	(Japanese)	Not identified	–	AD	Kobayashi[41]
	(French)	8qter and 1q25-31	–	AD	Baulac[42]
	(Belgian)	Not identified	–	AD	Depondt[43]
	(Japanese)	IL-1ß-511T allele	IL-1ß gene	AD	Kanemoto[81]

with a first simple febrile seizure: serum electrolytes, calcium, phosphorus, magnesium, complete blood count. Blood glucose should be determined only if the child had a prolonged obtundation post ictally. Serum electrolyte values may be abnormal in children after a febrile seizure, but this should be manifested by physical examination and history taking.[45]

Neuroimaging. According to the AAP practice parameter, a CT scan or MRI is not recommended in evaluating the child after a first simple febrile seizure.[45] Moreover, there are no data that supports the need for this test. In the study by Morales et al (1992),[48] 44 out of 164 children admitted to the hospital with febrile seizures had a CT scan. There were no abnormalities even though most had severe or focal febrile seizures. More data are needed in this area.

The workup of children with complex febrile seizures needs to be individualized. This often includes EEG and neuroimaging particularly if the child is neurologically abnormal.

Treatment. Generally, antiepileptic therapy, continuous or intermittent, is not recommended for children with one or more simple febrile seizures.[1] Parents should be counseled about the relative risks of recurrence of febrile seizures and recurrence of epilepsy, educated on how to handle a seizure, and should be given emotional support. If the seizure lasts for more than a few minutes then acute treatment with intravenous or rectal diazepam may be needed. Intravenous phenobarbital, phenytoin, or valproate may be needed for febrile status epilepticus. If the parents are very anxious concerning their child's seizures, intermittent oral diazepam can be given during febrile illness to help prevent recurrences.[1] In addition, antipyretics may comfort the child. Antiepileptic therapy may be considered for children with complex febrile seizures. Nevertheless, currently available data indicate that the possibility of future epilepsy does not change with or without therapy. Long-term management is summarized in **Figure 1**.

Intermittent therapy during fever. 1. Antipyretics. Through reducing fever, it is hoped that antipyretics would consequently reduce febrile seizure episodes. However, this is almost definitely not the case. Schnaiderman et al (1993),[49] compared

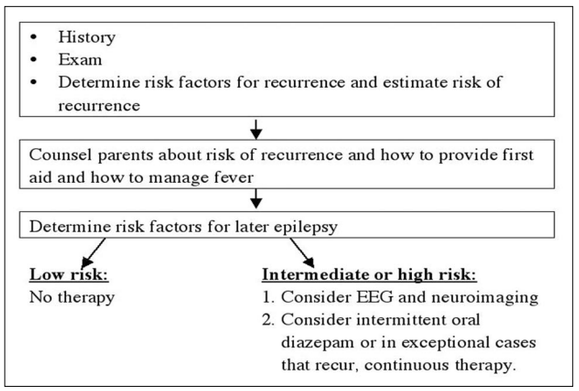

Figure 1 - Long-term management of febrile seizures.

ongoing prophylaxis of acetaminophen (every 4 hours) to sporadic doses (given only when the body temperature was 38°C or above) during a febrile illness. Neither regimens reduced the number of fever episodes or the duration of fever. In the study by Camfield et al (1990)[50] on 79 children with simple febrile seizures, acetaminophen was given during a febrile illness as 15 mg/kg every 4 hours with either daily phenobarbital or placebo. It was found that the acetaminophen and phenobarbital treatment reduced the recurrence of febrile seizures (5%), as compared to the acetaminophen and placebo regimen (25%). One explanation of the ineffectiveness of antipyretics in reducing febrile seizure recurrence might be that in some children, seizures occur at a somewhat low temperature and the antipyretic does not lower the temperature completely to normal.[51] In addition, febrile seizures often occur as the temperature is rising before antipyretics have had the chance to exert their effects. The study by Van Esch et al (1995),[52] compared acetaminophen 10mg/kg with ibuprofen 5mg/kg in preventing recurrence of febrile seizures in 70 randomized children. Although ibuprofen was more effective in reducing body temperature, no significant differences were found with respect to seizure recurrence (2 had recurrence after ibuprofen versus 3 after acetaminophen).[52]

2. Oral diazepam and other benzodiazepines. In the study by Autret et al (1990)[53] oral diazepam (0.5mg/kg, and then 0.2mg/kg every 12 hours during a febrile illness) was found to be ineffective in reducing febrile seizure recurrence (occurred in 16% of children) compared to placebo (19.5%). This was thought to be due to poor compliance by the parents.[53] Uhari et al (1995)[54] randomized 180 children into either diazepam and acetaminophen, diazepam and placebo, paracetamol and placebo, or 2 kinds of placebo. Diazepam was given as an initial rectal dose, followed after 6 hours by oral doses of 0.2 mg/kg tid for the first 2 days of a febrile illness (when body temperature is >38.5°C). Acetaminophen was given at a dose of 10 mg/kg 4 times per day. The 4 groups were followed for 2 years and compliance was excellent. In this study, the low doses of acetaminophen or diazepam and their combination was ineffective for febrile seizure prevention. Rosman et al (1993)[55] found that intermittent oral diazepam treatment (0.33mg/kg every 8 hours during fever) was effective as compared to placebo against febrile seizure recurrence in 406 randomized children with at least one febrile seizure. Results of 1.9 years follow up were that oral diazepam reduced the risk of recurrent febrile seizures by 44% per person-year. Difference in time to first recurrent febrile seizure was only significant after adjustment for covariates.[55] Intermittent oral nitrazepam, clobazam, and clonazepam (0.1/kg/day) have also been shown to be effective in reducing the risk of recurrence of febrile seizures.[56]

3. Rectal diazepam is usually used to stop ongoing seizures in hospital, or by parents at home. If used at home, parents are carefully instructed about the specific dose to be administered to the child. It has also been used as a prophylaxis to reduce recurrence at the time of febrile illness. In the study by Knudsen and Vestermark (1978),[57] children were randomized to either rectal liquid diazepam (0.5mg/kg every 12 hours) during illness or daily phenobarbitone. Both treatments were equally effective, or ineffective because there was no placebo, and adverse effects were minimal.[57] In the study by Lee et al,1986[58] intermittent diazepam prophylaxis 0.5 mg/kg administered as a rectal suppository every 8 hours for up to 48 hours when the temperature exceeded 38.5°C, was found to be as effective as continuous oral sodium valproate. Again, in this study also there was no placebo group.

Long-term antiepileptic drug (AED) therapy. In a recent meta analysis of 47 trials on AEDs and seizure prevention, phenobarbital was specifically found to be effective for prevention of recurrences of febrile seizures with a relative risk of 0.51 and a 95% confidence interval of 0.32-0.82.[59] In the placebo-controlled trial of Camfield et al (1990)[50] in children with a first simple febrile seizure, daily dose 4-5 mg/kg of phenobarbital was found to be effective in preventing recurrence (5% recurrence in the phenobarbital group versus 25% in the placebo group).[50] Another randomized study on 355 children with simple febrile seizure found that recurrence rate in intermittent phenobarbital therapy did not differ with the placebo while continuous treatment with phenobarbital was significantly better than placebo (6% versus 30% recurrence rate).[60] In the study by Farwell et al (1990)[61] in children with complex febrile seizures, where non-compliance was a problem, phenobarbital did not appear to have an advantage over placebo in reducing recurrence rate of seizures. After 2 years, 46% of the phenobarbital group had recurrence as compared to

38% in the placebo group.[61] In conclusion, most trials of phenobarbital have shown benefit of this drug in preventing recurrence or in reducing the number of febrile seizures on condition it is given daily, with compliance monitored and therapeutic blood levels maintained.[1] Bacon et al (1981)[62] compared phenobarbital, phenytoin, and placebo in children who had their first seizure before 2 years of age. Assessment was carried out after one year of treatment. Phenobarbital significantly reduced febrile seizure recurrence only in children who were less than 14 months of age at the time of their first febrile seizure, while phenytoin did not differ from placebo.[62]

Comparing children treated with phenobarbital and those treated with carbamazepine, the study by Anthony and Hawke (1983)[63] showed that 47% of the carbamazepine group had recurrence versus 10% of the phenobarbital group.[63] Another study showed that 13 of 16 children who have failed phenobarbital, had recurrent febrile seizures after 18 months of treatment with carbamazepine.[64] In the study by Lee and Melchior (1981),[65] phenobarbital did not show better outcome of seizure recurrence as compared to no treatment while valproic acid was significantly better, than both, in preventing recurrences. Herranz et al (1984)[66] found that phenobarbital 4.8mg/kg/d was effective in 80% of the patients and valproate 35.2 mg/kg/d was effective in 91.7% of the patients. Side effects after valproic acid (observed in 45% of patients) were significantly lower than after phenobarbital (76.7%). Several other studies have found valproic acid to be as effective as phenobarbital and significantly better than placebo.[56,67,68] The study by Mamelle et al (1984)[68] showed that treated children (with either phenobarbital or valproate) had significantly better seizure outcome than the placebo group. The study by Minagawa and Miura (1981)[69] found that a regimen of 20-25 mg/kg/d bid of valproic acid was less effective than a regimen of 30mg/kg/d bid and less effective than phenobarbital and primidone treatments. In a pooled analysis of trial results in Britain in 1988 for febrile seizures treatment, neither phenobarbital nor valproic acid was found to be effective.[70] However, more recently in 1998, a meta-analysis of randomized, placebo-controlled, published trials on prophylaxis for febrile seizures found that children receiving either phenobarbital or valproic acid had significantly lower risks of recurrence than placebo, while intermittent diazepam did not show significant advantage over placebo.[71]

Adverse effects of AED therapy. Cognitive and behavioral side effects are mostly encountered during phenobarbital treatment. Available data suggest that 20-40% develop behavioral adverse effects (hyperactivity, irritability, sleep disorders) and a smaller proportion suffer from idiosyncratic reactions.[1] Wolf et al (1981)[72] compared phenobarbital treated children with children receiving no therapy on psychometric tests (Weschler Preschool and Primary Scale of Intelligence WPPSI, the Matching Familiar Figures Test, and the Children's Embedded Figures Test). No significant differences were found on any scale at the initial evaluation or at the 3-month follow-up.[72] Farwell et al (1990)[61] documented a decline in intellectual ability of children receiving phenobarbital. They noted an average of 7.03 IQ points lower in children receiving phenobarbital as compared to the placebo group after 2 years of treatment. Six months after stopping the medication the IQ was still 5.2 points lower in the phenobarbital-assigned group. A continuation of the above study found that 3-5 years later, the difference in IQ was not significant. However, the phenobarbital group scored significantly lower on the reading achievement standard score of the Wide Range Achievement Test.[73] Hirtz et al (1993),[44] studied the effect of phenobarbital on total sleep time and night awakenings and found that only a subset of predisposed children had significant increases in night awakenings due to phenobarbital as compared to placebo. In the study by Knudsen and Vestermark (1978)[57] side effects including irritability, hyperkinesias and listlessness were documented in 45% of the patients. Herranz et al (1984)[66] observed side effects in 76.7% of the phenobarbital treated patients (13.3% required discontinuation of the drug) and 45% of the valproate patients (14.3% required discontinuation). Hyperactivity and sleep disturbances lead to discontinuation of phenobarbital in 21% of the patients in the study by Lee and Melchior (1981).[65] The study by Domizio et al (1993)[74] compared children in the phenobarbital treated group with those treated with other AEDs for side effects. In the phenobarbital group, 76% had behavioral disturbances (most commonly hyperactivity) as compared to 31% in the other group. According to the AAP practice parameter, reduced performance while on therapy with phenobarbital has been documented.

The use of Valproic acid in the treatment of febrile seizures has been discouraged because of fears of life-threatening liver toxicity in infants and children. It is specifically not recommended for routine use in children less than 3 years of age.[1] Thrombocytopenia, pancreatitis, and weight disturbances are other adverse effects encountered with valproic acid treatment. In the treatment of febrile seizures, valproic acid has been shown to cause vomiting and altered appetite as well as increased activity.[1,65]

In the study by Uhari et al (1995),[54] 39% of the children on intermittent oral diazepam (0.3 mg/kg) had moderately severe side effects of somnolence and ataxia. Rosman et al (1993)[55] documented that

25-30% of the children on intermittent oral diazepam developed ataxia, lethargy, and irritability, and 5% had speech abnormalities, sleep disorders, and altered activity. Furthermore, diazepam given at the time of febrile illness might mask an underlying infection by causing lethargy, which is usually attributed to the drug.[1]

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