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# Idiopathic epileptic seizures and syndromes in infancy

Idiopathic epileptic seizures and syndromes in infancy are important to recognise because they are age related and age limited. They do not occur in adults, are of excellent prognosis and anti-epileptic drug (AED) treatment is often unnecessary.

The infantile (in-fans = unable to speak) period is arbitrarily defined from 4 weeks (end of neonatal period) to 1.5 years (start of early childhood period) of life.

Febrile seizures are categorised among 'conditions with epileptic seizures that do not require a diagnosis of epilepsy'.[1–3]

The following are idiopathic epileptic syndromes with onset in infancy (Table 5.2):[1–3]

- epilepsy with febrile seizures plus (EFS+; see page 213)
- benign (familial and non-familial) infantile seizures (see page 215)
- myoclonic epilepsy in infancy (MEI; see page 217) (the word 'benign' was recently removed from the previous name 'benign myoclonic epilepsy in infancy' because, according to the ILAE report, 'this is not benign in some infants').[3]

## Febrile seizures

Febrile seizures[4–11] (a term preferred to febrile convulsions) are due to an age-related (6 months to 5 years) and predominantly genetic benign susceptibility to epileptic fits, precipitated by fever without evidence of intracranial infection or other cause. Children who have suffered a previous non-febrile seizure are excluded.

### Clarifications on classification

The 1989 classification of the ILAE categorised febrile seizures among the 'situation-related seizures',[1] which is synonymous with 'conditions with epileptic seizures that do not require a diagnosis of epilepsy' of the ILAE Task Force.[2] According to the new ILAE report, and with which I fully agree:

> *Febrile seizures:* Classically, the seizures that constitute this condition consist of two forms: simple and complex; however, many different types undoubtedly exist. This condition may eventually be understood to encompass many different entities.[3]

Seizures with fever in children who have suffered a previous non-febrile seizure are excluded[12] and the term 'febrile seizures' should be limited to an epileptic seizure precipitated by fever arising from

infection outside the nervous system in a child, aged from 6 months to 5 years, who is otherwise neurologically normal[13] (although the latter is not applicable in complex febrile seizures).

*Febrile status epilepticus* of longer than 30 min is either one long-lasting seizure or a series of shorter seizures where the infant fails to regain consciousness inter-ictally.[14–17]

## Demographic data

By definition, onset is strictly between 6 months and 5 years of age (peak at 18–22 months).[4,5,13] Boys slightly (60%) predominate. Prevalence is about 3% of children, but this is higher in certain ethnic groups (e.g. 7% for Japanese). The annual incidence rate is 460/100,000 children in the age group 0–4 years.[18]

## Clinical manifestations

> One minute he was a little boy with a cold and slight fever, lying on the sofa feeling miserable and the next his body was madly convulsing… It was very scary.
>
> *From an internet description by a father*

A rectal temperature level of at least 38°C (others propose 38.5°C) may be more important than a rapid rise of fever.[19] The majority (78%) of febrile seizures occur within the first day of the onset of fever;[7] they may occur before the fever is noticed or late in the course of a febrile illness.

The causes of fever vary and include upper respiratory tract infection or pharyngitis (38%), otitis media (23%), pneumonia (15%), gastroenteritis (7%), roseola infantum (5%) and non-infectious illness (12%). Viral diseases are more common, probably reflecting their higher prevalence in children. A particular association with influenza A has been emphasised.[20]

Seizures occurring soon after immunisation with diphtheria/pertussis/measles and tetanus vaccines are due to fever and not to an adverse effect of the vaccine. Furthermore, recent findings strongly support the view that cases of alleged vaccine encephalopathy could in fact be a genetically determined epileptic encephalopathy that arose *de novo*; *SCN1A* mutations were identified in 11 of 14 patients with alleged vaccine encephalopathy.[21]

### Seizures

*Generalised tonic–clonic seizures (GTCSs)* are by far the most common seizure type (80%). Tonic (13%), atonic (3%), unilateral or focal onset tonic–clonic seizures (4%) may occur in the remaining 20%. Rarely there may be only staring accompanied by stiffness or floppiness, rhythmic jerking movements without prior stiffening, focal stiffness or jerking. Febrile seizures with myoclonic jerks only (febrile myoclonic seizures) have a similar age of onset to other febrile seizures.[22–24]

Repetitive seizures in the same febrile illness occur in 16% of patients.

As a result of different prognostic implications, febrile seizures are categorised into simple and complex febrile seizures (Table 9.1).

*Simple febrile seizures* (70% of all) have strict inclusion criteria:

- they occur in neurologically healthy children aged between 6 months and 5 years
- the seizures are brief (<15 min) and generalised
- they happen only once during a 24-hour period of a febrile illness.[4,5]

*Complex febrile seizures* (also known as 'complicated' or 'atypical') are:

- prolonged (8%), lasting >15 min
- repetitive (11–16%) in clusters of two or more within 24 hours
- focal at onset or occur in children with perinatal psychomotor deficits (3.5–7%). These also include those with the exceptional Todd's post-ictal paresis (0.4%).

> A third of all febrile seizures may have one, two or all three of these complicating factors.[14,25–27]

Post-ictal symptoms other than drowsiness are rare and should raise the suspicion of another diagnosis.

**Simple febrile seizures versus complex febrile seizures**

| | Simple febrile seizures | Complex febrile seizures |
|---|---|---|
| Prevalence among febrile seizures | 70% | 30% |
| Neurologically normal | Inclusion criterion | Included but not necessary |
| With neurodevelopmental abnormalities | Exclusion criterion | 3.5–7% of all febrile seizures* |
| Age range | 6 months to 5 years | 6 months to 5 years |
| Duration <15 min | <15 min | Included but not necessary* |
| Duration >15 min or febrile status epilepticus | Exclusion criterion | 8% of all febrile seizures* |
| Once in a 24-hour period of a febrile illness | Inclusion criterion | Included but not necessary |
| Repetitive in clusters of two or more in a 24-hour period of a febrile illness | Exclusion criterion | 11–16% of all febrile seizures* |
| Generalised-onset tonic–clonic seizures (80% of all febrile seizures) | Inclusion criterion | Included but not necessary |
| Focal onset or focal epileptic seizures | Exclusion criterion | 4% of all focal seizures* |
| Post-ictal hemiparesis | Exclusion criterion | 0.4% of all febrile seizures* |
| Risk of subsequent epilepsy | Low (1%) | High (6–49%) |

Table 9.1 *A third of all febrile seizures may have one or all of these complicating factors.

### Risk factors of a first febrile seizure

The risk of a first febrile seizure is approximately 30% if a child has two or more of the following independent factors:[28,29]

- a first- or second-degree relative with febrile seizures
- a delayed neonatal discharge of >28 days of age
- parental reports of slow development
- day-care attendance.

### Risk factors for recurrence

Half the children will have one (32%), two (15%) or more (7%) recurrent seizures after a first febrile seizure. Half of those with a second febrile seizure will suffer at least one additional recurrence.

Recurrences are more likely when:

- the first febrile seizure occurs in the first year of life, during a short and low-grade febrile illness, or is complex
- there is a family history of febrile seizures in first-degree relatives
- there are persistent neurological abnormalities.

## Aetiology

Febrile seizures are often familial with a genetic predisposition.[30–32] Children with siblings or parents who have a history of febrile seizures are at a four- to fivefold higher risk than the general population. Boys are more susceptible than girls. Concordance rate is as high as 70% in monozygotic and 20% in dizygotic twins. The mode of inheritance is unknown, although this is probably polygenic. Autosomal recessive inheritance is unlikely because an excess of parents is affected and the risk to siblings is less than 25%.[14] Autosomal dominant inheritance is rare but well documented.

No definitive gene or locus for common febrile seizures has yet been established. In rare autosomal dominant kindreds of febrile seizures at least five different genetic loci were identified: 8q13-21,[33] 19p13.3 and 19q13.1,[34,35] 5q14-q15,[36] 6q22-q24[37] and 21q22.[38] Furthermore, genetic defects have been identified in the syndrome of epilepsy with febrile seizures plus (EFS+), which is characterised by

heterogeneous phenotypes of focal and generalised epileptic seizures (see page 213).

### Pathophysiology

The pathophysiology of febrile seizures is unknown. They constitute a specific response to fever irrespective of cause.

Evidence suggests the involvement of various sodium channels, $GABA_A$ receptors and additional auxiliary proteins in the pathogenesis of FS+ and even in simple febrile seizures.[30,32,39,40] A rare inherited cause – a mutation in the $GABA_A$ receptor subunit *GABRG2* gene – has been recently shown to cause a temperature-dependent intracellular trafficking defect.[41]

Circulating toxins and immune reaction products and viral or bacterial invasion of the CNS have been implicated, together with a relative lack of myelination in the immature brain and increased oxygen consumption during the febrile episode. Immaturity of thermoregulatory mechanisms and a limited capacity to increase cellular energy metabolism at elevated temperatures have been suggested as contributory factors.

The central histaminergic neuronal system may be involved in the inhibition of the seizures associated with febrile illnesses in childhood. Children in whom the histamine levels in cerebrospinal fluid do not rise during febrile illnesses may be susceptible to febrile seizures.[42]

A specific association between acute human herpesvirus 6 infection (roseola infantum) and febrile seizures has been postulated.[43]

## Diagnostic procedures

The main concern is to correctly diagnose 'febrile seizures' as opposed to 'seizures with fever', such as acute symptomatic febrile seizures and those occurring in the context of pre-existing epilepsy.

Febrile seizures do not require any investigations if the diagnosis is certain. The EEG and brain imaging are unhelpful and should therefore be discouraged.

### Electroencephalography

An EEG is not needed.[47] It is more likely to be normal or show non-specific abnormalities that may be overemphasised by inexperienced neurophysiologists. An EEG also does not have any predictive value for either the risk of recurrence of febrile seizures or the development of epilepsy.[47]

#### Important clinical note

The investigations done on a child with a simple or complex seizure during a febrile illness should be directed by the degree of illness and the suspected underlying infection.[11] Meningitis should be thoroughly considered and appropriately diagnosed or ruled out on clinical grounds and probably with a lumbar puncture, particularly in children under 2 years of age with or without meningism that show features of being unwell for a few days, vomiting, drowsiness, petechiae, decreased feeding, complex febrile seizures and, in particular, febrile status epilepticus.[11,44–46] Lumbar puncture may be mandatory in children who have a convulsion with fever in their first year of life (although this is still debatable).

## Differential diagnosis

Of immense clinical importance is the distinction of febrile seizures from 'convulsions with fever' such as in meningoencephalitis, and metabolic or neurodegenerative diseases.

A high index of suspicion for acute bacterial meningitis in the child with febrile convulsive status epilepticus is paramount. The classical symptoms and signs of acute bacterial meningitis may be absent in febrile convulsive status epilepticus.[46]

'Febrile seizures' should be clearly distinguished from 'seizures with fever', which are acute symptomatic febrile seizures caused by pyogenic or viral meningitis, herpes simplex encephalitis, other acute encephalitides, cerebral palsy with intercurrent infection and metabolic or neurodegenerative disease with a seizure precipitated by fever. Children who have a prolonged seizure or who have not

completely recovered within 1 hour should be suspected of having one of these conditions and investigated accordingly.[13]

Another main diagnostic issue is whether a first febrile seizure is a genuine febrile seizure or FS+ or the first manifestation of another genetically determined epileptic syndrome (see prognosis below). 'Atypical febrile seizures' is a common misdiagnosis of Panayiotopoulos syndrome (see Chapter 12).

The occurrence of non-febrile generalised convulsive seizures in association with viral gastroenteritis, without dehydration or electrolyte imbalance, have recently attracted interest both within[48,49] and outside of Asia.[50] This constitutes a benign condition; investigations may not be necessary and prognosis is excellent.

## Prognosis

Overall, children with febrile seizures have a sixfold excess (3%) of subsequent non-febrile seizures and epilepsy compared with controls.[25,26,51] Simple febrile seizures (70%) have only a twofold excess (1%). Significant risk factors for later epilepsy are shown in Table 9.2.

Non-febrile seizures start a few months to 30 years after the first one, but 85% start within 4 years. The risk is 2% by age 5, 4.5% by age 10, 5.5% by age 15 and 7% by age 25.[51] Conversely, children with no risk factors have a 2.4% chance of developing non-febrile seizures by the age of 25 years compared with 1.4% for the general population.[51] The rates are similar irrespective of the type of treatment for febrile seizures.[52]

Non-febrile seizures, if these occur, are of any type but generalised are more common than focal.[51]

Generalised non-febrile seizures tend to occur in children with frequent, brief, generalised febrile seizures and when there is a positive family history of non-febrile seizures.

Focal non-febrile seizures are likely in children with prolonged lateralised febrile seizures (20%), earlier onset and persisting neurological abnormalities.[51] The estimated risk of developing temporal lobe epilepsy (TLE) subsequent to prolonged febrile seizures is negligible, probably 1/75,000 children per year.[53,54] Conversely, a third of patients with hippocampal epilepsy have a previous history of prolonged febrile seizures (see mesial TLE with hippocampal sclerosis, page 385).[55]

Predisposition to both febrile seizures and other non-febrile epileptic syndromes is well documented. Febrile seizures precede the onset of various forms of epilepsies in 10–15% of children[54,56] (see individual syndromes of idiopathic generalised epilepsy [IGE] such as myoclonic epilepsy in infancy, benign childhood focal seizures such as rolandic and Panayiotopoulos syndrome, and other more severe forms of epilepsies such as Dravet syndrome). Also, pre-existing developmental hippocampal abnormality may predispose individuals to having prolonged febrile seizures.[57]

**Significant risk factors for later epilepsy**

**Significant risk factors for later epilepsy are:**

- Abnormal neurological or developmental status before the first febrile seizure
- Family history of non-febrile seizures
- Complex febrile seizures

**The risk after complex febrile seizures is:**

- 6–8% when a single complex feature is present
- 49% when all three complex features (prolonged, repetitive and focal febrile seizures) are present

Table 9.2

### Intellectual and behavioural outcome

Children with febrile seizures perform as well as other children in terms of their academic progress, intellect and behaviour.[58] The subsequent psychomotor development of children who were normal before the onset of febrile seizures remains normal.[58,59] If psychomotor deficits, learning difficulties and behavioural problems are found in children with febrile seizures, these are not related to the seizures, but probably reflect the overall developmental status of the child.[60]

## Management

This is based mainly on the recent recommendations of the American Academy of Pediatrics.[4,5]

### Acute management of a child with a febrile seizure

Control of the seizures is paramount. Long-lasting febrile convulsive seizures (>10 min) or status epilepticus (>30 min) is a genuine paediatric emergency that demands appropriate and vigorous treatment, similar to non-febrile convulsive status epilepticus (Chapter 3).[17,52] Early, usually parental, treatment is more effective than late emergency treatment.[52] The parents of children with recurrent seizures should be advised to place the child on his or her side or stomach on a protected surface and administer a preparation of rectal benzodiazepine. In an emergency facility, the child's airway should be kept clear, oxygenation maintained, and intravenous or rectal benzodiazepines given to halt the seizure (Table 3.3).

*Diazepam* intravenously at a dose of 0.25–0.5 mg/kg, or in rectal preparations at a dose of 0.5 mg/kg, is probably the first choice (page 79). Rectal absorption of liquid diazepam is very rapid; it reaches the brain within minutes and has an almost intravenous efficacy. A disadvantage of diazepam is its short duration of action.

*Lorazepam* administered intravenously (0.1 mg/kg), which is less likely to cause respiratory depression and probably has a longer duration of action than diazepam, is often preferred in medical facilities (page 80).

*Midazolam* administered by buccal (0.4–0.5 mg/kg) or intranasal (0.2 mg/kg) application has superior efficacy to diazepam[61,62] and is becoming the drug of choice for terminating prolonged seizures in the home (page 80).[63,64]

Treatment of the fever and, mainly, the underlying illness is also important. Antipyretic treatment during febrile illnesses does not reduce the recurrence rate and cannot be recommended other than to make the child more comfortable and avoid dehydration. Paracetamol is more widely used than ibuprofen, whereas aspirin is avoided because it has been associated with the development of Reye syndrome.

Physical methods of reducing the fever such as sponging with tepid water, fanning and cold bathing have a quicker but shorter effect than antipyretics. However, they are likely to cause discomfort and are not usually recommended in the UK.[13]

### Prophylactic management

The best treatment for children with a first febrile seizure is education and reassurance for the parents.[65]

Simple febrile seizures do not need prophylactic treatment. The risks are small and the potential side effects of drugs appear to outweigh the benefits.

Prophylactic treatment may be desired if a child has one or, mainly, a combination of the following features:

- complex febrile seizures
- neurological abnormalities
- age <1 year
- frequent recurrences.

Prophylactic treatment may be continuous or intermittent at the time of a febrile illness. Neither of these may be needed for most children with febrile seizures, who almost invariably do well.

*Continuous treatment* consists of daily administration of, mainly, phenobarbital (which at a blood level of 15 µg/ml can effectively reduce the risk of recurrences) and, less often, valproate (fatal hepatitis in this age group or pancreatitis make valproate probably unacceptable). Carbamazepine and pheny-

toin are ineffective in the prevention of febrile seizures.[4,5]

*Intermittent treatment* at the time of a febrile illness, mainly with rectal or oral diazepam, is an alternative to continuous medication (again a debatable issue). There is a small reduction in the recurrence risk with a dose of diazepam 0.3 mg/kg, although a third of children will have significant side effects of somnolence or ataxia.

These recommendations need updating with regard to the AEDs used; for example, many physicians are, rightly, reluctant to prescribe phenobarbital.

### Supportive family management

A total of 47% of parents thought that their child was dying during the initial febrile seizure.[66]

The parents of young children should have general information provided by the family doctor about fever and febrile seizures. Parents who have watched their child during a fit need specific information in order to avoid long-term reactions.[67,68]

Supportive family management includes education about febrile seizures and providing specific instructions about antipyretic and anti-epileptic prophylaxis and emergency procedures for possible subsequent seizures.

# Epilepsy with febrile seizures plus

*Synonyms:* generalised epilepsy with FS+ or autosomal dominant epilepsy with FS+.

*'Febrile seizures plus'* is a term to denote childhood-onset febrile seizures, which (unlike the typical febrile seizures) start earlier (from less than 6 months with a mean of 1 year) than the classical febrile seizures. They are often multiple and continue beyond the age of 5 years, usually remitting by mid-childhood (median 11 years). Individuals with FS+ may also have additional non-febrile seizures. In some children with FS+, seizures with fever occur beyond age 5 years, whereas in others, all seizures beyond age 5 years are non-febrile.[69–75]

*Epilepsy with febrile seizures plus (EFS+)*[39,40,69–75] is the most important familial epileptic syndrome because it links febrile seizures with various other epileptic seizures and syndromes, and documents genetic relationships between the benign and severe and the focal and generalised epileptic disorders.

## Clarifications on classification

EFS+, described by Berkovic and his associates,[69–75] was initially recognised by the ILAE as a syndrome in development.[2] Now, the new ILAE report recognises 'febrile seizures plus as an epileptic condition that is part of the familial syndrome known as EFS+. The latter is broader than a single generalised syndrome and may be a useful category for future classifications.'[3]

The name EFS+ is preferred to the other synonyms because (1) the spectrum of the syndrome includes diverse types of focal and generalised seizures[77] and (2) autosomal dominant inheritance in EFS+ might be rare, and most of EFS+ display a complex pattern of inheritance.[74]

## Demographic data

The age at onset, from the first months of life to childhood, varies considerably between individuals, even individuals of the same family. As a rule, FS+ usually start 6 months earlier than the classical febrile seizures. Both sexes are equally affected. The prevalence is unknown, but may be high considering the increasing numbers of publications and the very broad spectrum of EFS+.

## Clinical manifestations

The syndrome of EFS+ is characterised by heterogeneous clinical phenotypes. By definition, in all

families some patients have FS+, which are often preceded by classical febrile seizures.

Typical febrile seizures and FS+ are the most common clinical phenotypes that may occur alone (75% of affected patients) or in combination with other types of seizures, including:

- brief non-febrile generalised convulsions
- other generalised seizures, such as absences, myoclonic jerks, tonic seizures and, more frequently, myoclonic–atonic seizures
- focal seizures of mainly frontal or temporal lobe origin may occur[78] in approximately 13% of affected individuals,[79] and these focal seizures may dominate in some members of affected families.[77]

EFS+ shows marked genetic and phenotypic heterogeneity. There are extreme intra- and inter-familial clinical variations with regard to seizure type, seizure frequency, severity and prognosis. Within the EFS+ spectrum, more severe syndrome phenotypes can occur including Dravet syndrome, epilepsy with myoclonic–astatic seizures (EM-ASs) and TLE.[80,81]

## Aetiology

EFS+ is a purely genetic disorder with profound heterogeneity. Inheritance was considered generally autosomal dominant with incomplete penetrance,[76] but this may not be the only situation.[82] In fact more recent studies indicate that autosomal dominant inheritance is rare. A more complex pattern of inheritance is emerging.[74]

EFS+ is genetically heterogeneous with two loci described on chromosome 19q (*GEFS+*) and chromosome 2q (*GEFS2*). Mutations were found in the *SCN1A*, *SCN1B* and *SCN2A* genes (encoding the $\alpha_1$, $\alpha_2$ and $\beta_1$ voltage-gated sodium channel subunits) and the *GABRG2* gene ($GABA_A$-receptor $\gamma_2$-subunit).[83] More recent studies have indicated that mutations of *SCN1A*, *SCN2A*, *SCN1B* and *GABRG2* in patients with EFS+ are rare.[79]

There may be many mechanisms by which sodium channel alterations cause the various clinical phenotypes of EFS+. There is a possibility of simultaneous involvement of multiple genes for the seizure phenotypes.[74] To produce the different seizure types observed in families with EFS+, seizure predisposition determined by the EFS+ genes could be modified by other genes and/or environmental factors.[81]

## Diagnostic procedures

Brain MRI is normal. The EEG findings are diverse and depend on the clinical phenotype.[73] Half of the patients have normal EEGs. The most common EEG abnormality is sparse and brief generalised polyspike–wave discharges (GPSWD) or generalised spike–slow-wave discharges (GSWD) that might require sleep EEGs for their detection. In patients with focal seizures, the EEG shows focal sharp waves, which are mainly localised in the frontal and temporal regions.[77,79]

In EM-AS and Dravet syndrome the EEG abnormalities are severe, as described in the relevant chapters.

## Differential diagnosis

The main diagnostic issue is whether a first febrile seizure is a classical febrile seizure or FS+; however, they are usually impossible to differentiate initially. It is only when at least two febrile seizures occur outside the age range of classical febrile seizures (i.e. earlier than 6 months or later than 5 years) that a diagnosis of FS+ is certain.

Distinguishing features of the EFS+ syndrome are the persistence of febrile seizures beyond the age of 5 years, the occurrence of non-febrile seizures and family history.

Absences, when they are present, are usually brief, mild and easily distinguishable from the severe absences of childhood or juvenile absence epilepsy.

The evolution to severe phenotypes such as EM-AS or Dravet syndrome[84] be comes apparent only with the emergence of non-febrile seizures compatible with these disorders.

## Prognosis

Overall, EFS+ was initially considered benign and self-limited.[76,84] Non-febrile seizures occur in about a quarter of patients and these are usually infrequent and often remit by mid-childhood (a median of 11 years). However, this overall good prognosis is now reconsidered, particularly since the inclusion of Dravet syndrome[84] and EM-AS, among EFS+.

## Management

Repetitive febrile seizures or FS+ may require prophylactic treatment (see Chapter 7). Treatment of more severe phenotypes has been described in the relevant sections.

# Benign infantile seizures

*Synonym:* Watanabe–Vigevano syndrome.

Benign infantile seizures, familial and non-familial,[85–93] constitute a benign age-related idiopathic syndrome of infancy. The seizures are focal and the infants are otherwise normal. Watanabe described the non-familial forms[85] and Vigevano the familial forms.[86]

## Considerations on classification

The ILAE diagnostic scheme initially recognised two types of benign infantile seizures (familial and non-familial) (Table 5.2).[2] However, as I have previously proposed,[94] these are now unified in one syndrome in the new ILAE report:[3]

> The familial and non-familial forms of benign infantile seizures are identical except for the family history. Consequently, the sporadic form cannot be considered a separate syndrome, and both should be combined into a single syndrome, unless subsequent information indicates otherwise.[3]

## Demographic data

Age at onset is from 3 to 20 months with a peak at 5 or 6 months. The familial form mostly starts between 4 and 7 months. Boys and girls are equally affected in the sporadic form, but more girls are reported in the familial cases. Only small numbers, about 100 of all types, have been reported so far but this may increase with improved awareness of the condition.

## Clinical manifestations

Seizures characteristically occur in clusters of five to ten per day for 1–3 days and may recur after 1–3 months. A third of patients have single isolated seizures 10–15 days before the clusters occur.

The seizures are focal, predominantly diurnal and brief (0.5–3 min). Longer seizures (3–6 min) occur at the beginning of the clusters and in the familial cases.

The seizures manifest with motor arrest, impairment of consciousness with decreased responsiveness, staring, eye and head deviation, and mild unilateral clonic convulsions. Simple automatisms are frequent. Alternating from one side to the other is common. The seizures may progress to hemiconvulsions or generalised convulsions.

## Aetiology

The familial form is most probably autosomal dominant with genetic heterogeneity. Linkage has been found to chromosomes 19q12-13.1,[95] 2q24[96] and 16p12-q12.[97]

Benign familial infantile seizures do not appear to have genetic links with benign neonatal seizures, although these may also prove to be channelopathies.

Of significant genetic interest is the description of familial forms with seizure onset in the intermediate age (1–3 months) between benign neonatal and infantile seizures, as well as familial infantile convulsions in families with choreoathetosis[98,99] or hemiplegic migraine.

*Benign familial neonatal–infantile seizures*[100] is an autosomal dominant disorder starting between the ages of 2 days and 7 months with non-febrile focal seizures of mainly posterior onsets, which remit by 12 months. The disorder is a sodium channelopathy caused by mutations in the sodium channel subunit gene *SCN2A*.[100] No such mutations were found in ten families with benign familial infantile seizures.[100]

*Familial infantile convulsions and choreoathetosis* are an autosomal dominant disorder with benign infantile seizures together with variably expressed paroxysmal choreoathetosis.[97–99,101,102]

*Familial hemiplegic migraine and benign familial infantile seizures*[103] partially cosegregate in some rare families with novel missense mutations in the *ATP1A2* $Na^+/K^+$-ATPase pump gene on chromosome 1q23.[104]

The sporadic cases of benign infantile seizures may be identical to the familial ones, but with reduced expressivity, or they may be due to exogenous factors such as rotavirus infections.[105]

## Diagnostic procedures

All relevant tests applied for infantile seizures are normal. However, they are needed, particularly for the sporadic cases, in order to exclude symptomatic infantile seizures.

### Electroencephalography

The inter-ictal EEG is normal. The ictal EEG demonstrates focal discharges of fast activity mixed with spikes that usually spread to neighbouring areas or the whole brain (Figure 9.1).[105–107] Onset may be

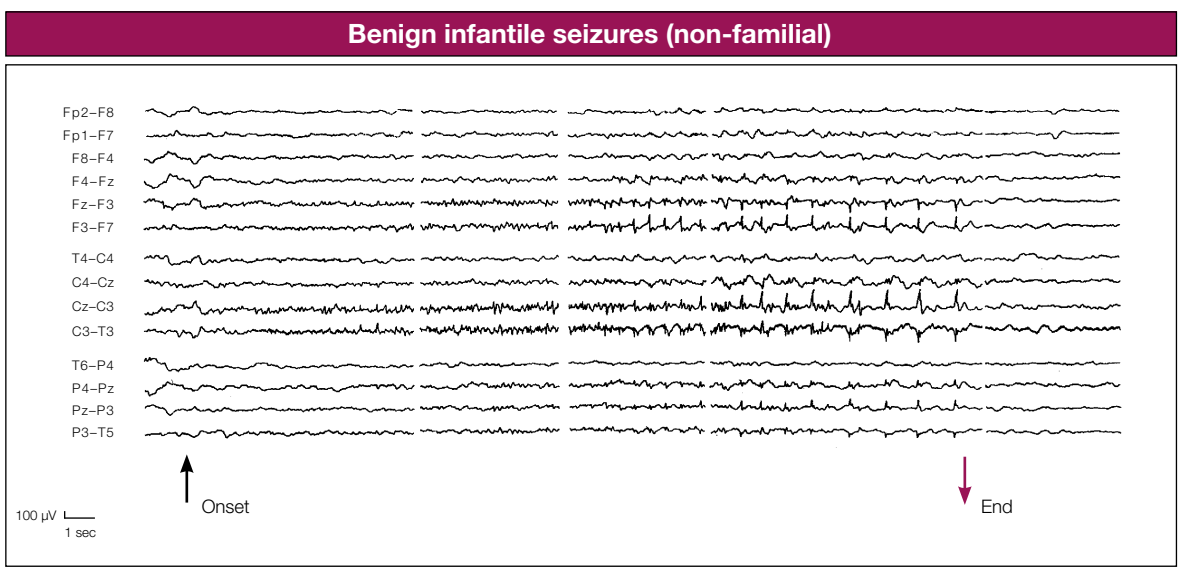


**Figure 9.1** An ictal EEG of a seizure in an 8-week-old baby who, at this age, had three focal seizures of right-sided convulsions involving the face and upper limbs (see case 17.2 in Panayiotopoulos[107]). Brain MRI was normal. The inter-ictal EEG was normal. Subsequent EEGs were normal and treatment stopped at age 10 months. He was well until the age of 7 years when he started having typical rolandic seizures. One year later, he developed epilepsy with continuous spikes and waves during slow-wave sleep (Figure 10.12). The arrows mark the onset and termination of the seizure. Note the ictal EEG onset with focal left-sided fast spikes of low amplitude.

frontal, temporal, parietal or occipital, and may vary in location and side between seizures of the same patient.[106]

## Differential diagnosis

This may be difficult in the sporadic form, which requires a long follow-up before such a diagnosis can be established. Other syndromes with familial benign infantile seizures should be considered.

## Prognosis

Prognosis is usually good.[108,109] Seizures remit within 1 to 2 years of onset. Development is normal. In untreated cases there can be isolated or brief clusters of seizures within this period.

## Management

In the active seizure period, AED treatment is usually effective. Complete seizure control is achieved in almost all cases. Recurrences after 1 or 2 months may occur in a third of patients, but these are also easily controlled by drug dose adjustments. AEDs are usually withdrawn after 1–3 years with no relapses. Watanabe mainly used carbamazepine, whereas Vigevano used valproate or phenobarbital. Benzodiazepines or phenobarbital are insufficient for the cessation of clustered seizures.[110]

# Myoclonic epilepsy in infancy

Myoclonic epilepsy in infancy (MEI)[111–123] is probably the earliest form of an age-dependent IGE syndrome and is manifested mainly or exclusively by just myoclonic jerks. The jerks may be spontaneous, reflex or both.

## Clarifications on classification

The recent report of the ILAE Classification Core Group deleted the word 'benign' from benign MEI 'because this is not benign in some infants'.[3] However, this may be premature without defining exactly what this syndrome is and particularly whether those with reflex myoclonic jerks (reflex MEI) are truly separate from those with spontaneous myoclonic jerks only. Furthermore, it should be the majority rather than a 'few cases' that determine the overall features and prognosis. Even the most benign medical conditions may infrequently develop to an unfavourable prognosis (e.g. seasonal viral flu).

## Demographic data

Onset is between 6 months and 3 years, but in a few infants it may start earlier (4 months) or later (4 to 5 years). Boys are twice as likely to be affected as girls. The prevalence may be around 1% or 2% of all epilepsies starting before the age of 3 years.[117] This syndrome is based on retrospective studies and single case reports of approximately 100 patients, sometimes heterogeneous and including those with stimulus-elicited (reflex) myoclonic jerks.[117]

## Clinical manifestations

Myoclonic seizures are the predominant and often the only type of fits in MEI. They mainly affect the head, eyeballs, upper extremities and the diaphragm (Figure 9.2). The jerks are brief and singular or clusters that vary in frequency and violence. They manifest clinically with head nodding and, more rarely, flexion or extension of the body. The upper limbs usually fling upwards and outwards, whereas the eyeballs may

## A typical patient with MEI with myoclonic jerks only and excellent prognosis

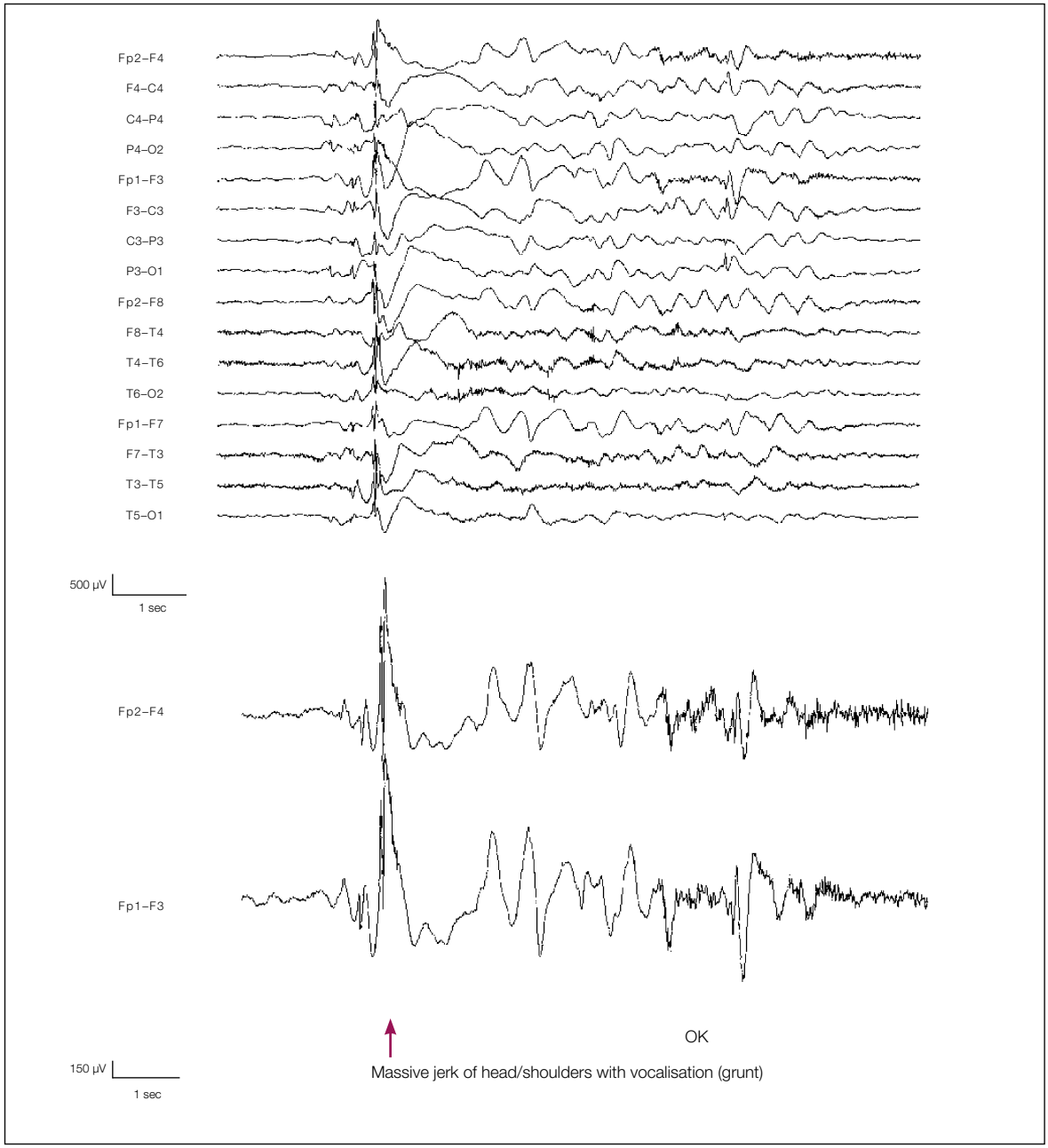


**Figure 9.2** At age 3 years, this girl developed frequent and violent myoclonic jerks mainly in the head and shoulders with grunting noises. She was referred for a routine EEG 6 weeks from the onset of the jerks. On the basis of the history, the EEG technician applied video-EEG recording and deliberately extended the recording for clinical events. Two electroclinical seizures were captured, one of which is shown in this figure. Clinically, the first symptom was a sudden jerk of the head and shoulders backwards. This coincided with a giant (approximately 1 mV) spike or multispike–slow-wave followed by rhythmic slow activity at around 3–5 Hz, together with some random spikes and slow waves. The whole discharge lasted for approximately 5–7 s. The seizures stopped only when clonazepam was added to valproate (valproate was probably not needed). Subsequent serial EEGs were normal. At age 6 years she was no longer on medication, had developed well, was free of seizures and had a normal EEG.

roll upwards. A brief yell, probably resulting from the contraction of the diaphragm, sometimes accompanies the jerks. Falls may occur in the rare event that the lower limbs are affected. Myoclonic jerks may sometimes be very mild and inconspicuous.

Consciousness is commonly intact, but clusters of jerks may be associated with mild clouding.

Myoclonic seizures are usually spontaneous, occurring randomly in alert stages and exaggerated by drowsiness and NREM sleep. In some patients they tend to cluster on awakening or during the first hours of sleep. Reflex myoclonic jerks are sometimes prominent. Patients may have spontaneous or reflex-only jerks, or both.

The duration of the jerks is usually brief (1 or 2 s). Some children have marked clusters of generalised clonic seizures, exclusively during sleep or on awakening, which are prolonged by up to 15–20 min and can cause cyanosis without loss of consciousness.[112]

*Other types of seizures:* A fifth of patients have simple, brief and infrequent febrile seizures, usually preceding the onset of myoclonias.

A fifth of the patients may develop infrequent GTCSs, usually in their early teens.

Non-febrile seizures of uncertain categorisation, before the onset of myoclonic seizures or during the clinical course of the disease, have been reported.[113]

In one report, 6 of 11 children also had non-epileptic myoclonus.[124]

### Precipitating factors

A fifth of patients have clinical and EEG photosensitivity.[111,116,122,123,125] In 10% the myoclonic jerks are predominantly or exclusively elicited by unexpected acoustic or tactile stimuli, and these may be of a better prognosis.[111,116,126,127] Single jerks or clusters of two to eight symmetrical limb jerks, mainly of the arms, are elicited by sudden noise or tactile stimuli when either awake or asleep. Startle is important. If expected the stimulus is ineffective.[111]

## Aetiology

MEI is probably the earliest form of an IGE. There is no evidence that it is linked with juvenile myoclonic epilepsy or indeed any other type of IGE. A family history of epilepsy or febrile seizures is present in 30% of cases.

Familial MEI with autosomal recessive inheritance and linkage to chromosome 16p13 has been reported in one family, but in this case myoclonic seizures persisted into adulthood and all patients developed GTCSs in their early teens.[128]

## Diagnostic procedures

All tests other than EEGs are normal. The inter-ictal EEG is normal. Spontaneous, inter-ictal GPSWD without associated jerks are exceptional.

The ictal EEG during jerks shows GPSWD or GSWD with a duration of 1–3 s (Figure 9.2). Frequently, ictal EEG discharges are limited to the rolandic and vertex regions.[121]

Drowsiness and early stages of sleep exaggerate the EEG discharges that may occur with or without jerks. EEG generalised discharges of mainly multiple spikes with jerks are often stimulus evoked by photic stimulation or unexpected acoustic or tactile stimuli. These occur in the awake or sleep stages.

## Differential diagnosis

MEI should be differentiated from non-epileptic conditions such as hypnagogic jerks and Fejerman syndrome (benign non-epileptic myoclonus, page 94). Hypnagogic jerks do not occur in waking states and the EEG is normal. Benign non-epileptic myoclonus resembles epileptic spasms rather than the myoclonic jerks of MEI.

It should not be difficult to differentiate MEI from epileptic encephalopathies such as West, Dravet or Lennox–Gastaut syndrome with multiform seizures, severe EEG abnormalities and often neurodevelopmental deficits.

## Prognosis

Remission usually occurs between 6 months and 5 years of onset. Patients with jerks provoked by auditory or tactile stimuli have a better prognosis, and the jerks are easily controlled with AEDs and

avoidance of precipitating factors. Conversely, EEG photosensitivity may persist many years after clinical remission.

In general, 10–20% of patients with MEI develop infrequent GTCSs in their early teens when medication has been withdrawn.

Psychomotor development is often normal, but 10–20% of children may later develop mild (usually) cognitive, behavioural or motor deficits, particularly if untreated.

## Management

The response to AED treatment is usually excellent. Patients with photosensitivity are more difficult to control. Patients with auditory and somatosensory evoked myoclonus may not require treatment or withdrawal from AEDs may be initiated after 1 year.

With valproate, 80% of patients become seizure free. However, no other suitable AEDs have been tried in this condition. This should include monotherapy with small doses of:

- clonazepam, which is more effective than valproate in controlling myoclonic jerks
- levetiracetam, which is the most potent new anti-myoclonic drug and which also significantly suppresses photosensitivity).

AED withdrawal should be slow.

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