

Benign pediatric localization-related epilepsies

Part I. Syndromes in infancy

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Received June 10, 2006; Accepted August 2, 2006

ABSTRACT – There is currently increasing interest in identifying and classifying pediatric benign epilepsy syndromes and recently several new syndromes have been recognized. Benign epilepsy syndromes, by definition, occur in children with normal developmental history, respond well to therapy, and remit without sequelae. The large majority of children with benign epilepsy syndromes follow a truly benign course. The concept of benign epilepsy syndromes has, however, been challenged by the minority of patients who continue to have seizures despite therapy, develop new seizures after initial remission, or exhibit neuropsychological abnormalities. Without long-term follow-up, benignity can not be truly ascertained *a priori*. Thus it may be preferable to use the terms *possible* and *probable* before the name of a specific syndrome until such time that the diagnosis of a definite benign syndrome is confirmed on long-term follow-up. In this review of the pediatric benign localization-related epilepsy syndromes, we address the concept of benignity and the process of diagnosis of a benign epilepsy syndrome. In addition we review the epidemiology, clinical manifestations, EEG findings, work-up, diagnostic criteria, differential diagnosis, genetics, management and prognosis of benign infantile familial convulsions, benign partial epilepsy in infancy with complex partial seizures, benign partial epilepsy in infancy with secondarily generalized seizures, benign infantile convulsions associated with mild gastroenteritis, and benign infantile focal epilepsy with midline spikes and waves during sleep.

Key words: benign epilepsy, benign infantile convulsions, benign partial epilepsies, infancy

Concept of a benign epilepsy syndrome

Historical review of the concept of benignity

That certain children with seizures follow a benign course has been recognized for over two centuries. A number of benign epilepsy syndromes were defined and this concept evolved even further in the seventies and eighties. For example, in 1977, Lombroso and Fejerman (1977) recog-

nized that some infants with myoclonic seizures follow a clearly benign course, in marked contradistinction to infants with infantile spasms. Later, Freeman *et al.* (1987) distinguished “benign developmental seizures” or “benign epilepsy of childhood” from other seizure syndromes based on the observation that many children with certain seizures have a benign developmental disorder which lowers the CNS threshold to seizures, and which is “outgrown” as their CNS matures. More recently several new benign

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epilepsy syndromes have been described. In addition, the concept of a benign epilepsy syndrome was developed further and was defined as “a syndrome characterized by epileptic seizures that are easily treated, or require no treatment, and remit without sequelae” (Engel 2001).

Over the past two decades there have been intensive efforts to characterize the benign localization-related epilepsy syndromes of infancy and childhood and delineate their genetic features. Data over the years have shown that the designation of many syndromes as “benign” is useful to a large extent: The diagnosis of a benign syndrome allows for the prediction of a likely good prognosis, and can also aid in the choice of therapy and its duration. The majority of patients either remit spontaneously or respond well to therapy, have no seizure recurrence, and have normal developmental outcome. However, a minority of patients initially diagnosed as having a benign syndrome will not follow a benign course. Some of these may not remit with treatment, have seizure recurrence, or exhibit permanent cognitive compromise or other neurologic sequelae. Thus, the concept that a benign syndrome is consistently easily treated and that it consistently remits without sequelae has been challenged (Echenne *et al.* 2001).

Various factors, singly or in combination, may explain the less benign course followed by some patients. There may be a coexistence of two diseases, for example, BECTS and temporal lobe epilepsy. Patients may also manifest initially with a benign syndrome and later with a more severe one (Choueiri *et al.* 2001). In addition, what appears to be a benign syndrome may be the manifestation of a symptomatic epilepsy such as secondary to meningitis. Moreover, some cases of true benign epilepsy may simply be less benign than others. Finally, the use of inappropriate medications, or even an appropriate medication that inadvertently exacerbates an epilepsy syndrome, may lead to

progression of an initially benign clinical course (Kikumoto *et al.* 2006, Prats *et al.* 1997).

Benign epilepsy syndromes in infancy

Benign epilepsy syndromes in infancy include benign infantile familial convulsions (BIFC), benign partial epilepsy in infancy with complex partial seizures (BPEI-CPS) and benign partial epilepsy in infancy with secondarily generalized seizures (BPEI-SGS), benign infantile convulsions associated with mild gastroenteritis, and the newly defined benign infantile focal epilepsy with midline spikes and waves during sleep (BIMSE) [previously known as benign partial epilepsy in infancy and early childhood with vertex spikes and waves (BVSE)] (see *table 1* for abbreviations used).

BIFC patients followed-up into childhood have shown no seizure recurrence, EEG normalization, and exhibit normal psychomotor development in the large majority of cases, with the exception of mild mental retardation in one case (Vigevano *et al.* 1994). Among patients diagnosed as having BPEI-CPS or BPEI-SGS at initial presentation, 76 % (Okumura *et al.* 2000) to 85 % of patients (Okumura *et al.* 2006a) continue to meet the criteria for a benign syndrome on follow-up into early or late childhood. In a minority, a less benign course is reported, with lack of seizure resolution, the development of more severe epilepsy syndromes, and/or most commonly the occurrence of psychomotor delay. There appears to be no subsequent risk of seizure recurrence or neurodevelopmental delay in patients with a history of benign infantile convulsions associated with mild gastroenteritis and BIMSE (Komori *et al.* 1995, Capovilla and Beccaria 2000, Capovilla *et al.* 2006) though long-term follow-up into adolescence of large numbers of patients is not yet available.

Table 1. Abbreviations used.

ADNFLE	Autosomal dominant nocturnal frontal lobe epilepsy
BCEAS	Benign childhood epilepsy with affective symptoms
BCEOP	Benign childhood epilepsy with occipital paroxysms
BECTS	Benign childhood epilepsy with centrotemporal spikes
BFNIC	Benign familial neonatal-infantile seizures
BIFC	Benign infantile familial convulsions
BPEI	Benign partial epilepsy in infancy
BPEI-CPS	Benign partial epilepsy in infancy with complex partial seizures
BPEI-SGS	Benign partial epilepsy in infancy with secondarily generalized seizures
BIMSE	Benign infantile focal epilepsy with midline spikes and waves during sleep*
ECSWSS	Epilepsy with continuous spike and wave during slow wave sleep syndromes
FHM	Familial hemiplegic migraine
ICCA	Infantile convulsions and choreoathetosis

*Previously known as benign focal epilepsy with vertex spikes and waves during sleep (BVSE) (Capovilla *et al.* 2006).

Benign epilepsy syndromes in childhood

The benign localization-related epilepsies of childhood include benign childhood epilepsy with centrotemporal spikes (BECTS), also referred to as benign rolandic epilepsy, benign childhood epilepsy with rolandic spikes and sylvian seizures, benign childhood epilepsy with occipital paroxysms (BCEOP), or idiopathic epilepsy with occipital paroxysms, and the rare benign partial epilepsy with extreme somatosensory evoked potentials and benign childhood epilepsy with affective symptoms (BCEAS), or benign psychomotor epilepsy.

The natural course of BECTS is one of resolution by mid-adolescence (Wirrell 1998). Ninety-eight percent (Loiseau *et al.* 1998) to 99.8% (Bouma *et al.* 1997) of cases will be in remission by the age of 18. However, the relative risk of subsequent GTCS in BECTS patients was found to be ten times more likely as compared to the general population (Loiseau *et al.* 1998). Less than 1% of patients with BECTS will go on to develop atypical benign focal childhood epilepsy (ABFCE) also known as pseudo-Lennox-Gastaut (Hahn 2000), epilepsy with continuous spikes and waves during slow sleep syndrome (ECSWSS), or Landau-Kleffner Syndrome (LKS) (Fejerman *et al.* 2000). In 50-60% of Panayiotopolous type-BCEOP, remission typically occurs within 1-2 years of seizure onset (Panayiotopoulos 1999a). The majority of Panayiotopolous type-BCEOP patients remit by age 12 (Oguni *et al.* 1999). In approximately 5% of patients with Panayiotopolous type-BCEOP, BECTS will later occur and will remit by the age of 16 (Koutroumanidis 2002, Oguni *et al.* 1999, Berg and Panayiotopoulos 2000, Caraballo *et al.* 1998). In 50-60% of patients with Gastaut type-BCEOP, remission generally occurs within 2-4 years. In 30-40% of cases, visual seizures with or without secondarily generalized GTCS continue to occur, particularly without treatment (Panayiotopoulos 1999a). Intellectual outcome following seizure remission is generally normal, though mild intellectual impairment has been reported to occur in a minority of patients with either type of BCEOP (Oguni *et al.* 1999, Verrotti *et al.* 2000). The majority of patients with BCEAS become seizure free, though seizures may persist despite AED therapy (Dalla-Bernardina *et al.* 1992).

Several investigators have attempted to define the characteristics of those patients that will not follow a benign course. Such studies have not been able to completely define such characteristics. At this time, long-term follow-up is the only means of definitively confirming the benignity of a patient's syndrome.

Proposed scheme to the diagnosis of benign epilepsy syndrome

Thus, based on the above, it can be argued that until the patient is followed-up and the epilepsy remits the diagnosis of a benign syndrome is still presumptive. We thus propose the concepts of a "possible", "probable", and

"definite" diagnosis of a benign epilepsy syndrome is most suitable until long term follow-up is available (*figure 1, table 2*). As such, the diagnosis of a *probable benign epilepsy syndrome* would be given if the patient has clinical and EEG features consistent with a benign syndrome, negative prenatal, perinatal, and postnatal history, and normal laboratory and neuroimaging. If the patient has atypical features (e.g. does not respond to initial AED therapy), the diagnosis given is that of a *possible benign epilepsy syndrome*. It is only after long-term follow-up, with no seizure recurrence, consistently normal neuropsychological function, and no sequelae, that a diagnosis of a *definite benign epilepsy syndrome* would be made. Of note is that some patients with atypical features or abnormal MRI findings or with neurologic deficits may still manifest the findings and course of a benign syndrome and in those, should long term follow-up be consistent with a benign syndrome, the atypical features are usually considered incidental.

In this first part of our two-part review on the pediatric benign epilepsy syndromes, the epidemiology, clinical manifestations, EEG findings, work-up and diagnostic criteria, differential diagnosis, genetics, and management and prognosis of the benign epilepsy syndromes of infancy are reviewed. In addition, an overview of the genetics of the localization-related epilepsy syndromes is presented (see *table 1* for abbreviations used).

Familial benign localization-related epilepsy syndromes of infancy

Benign infantile convulsions occur in familial and non-familial (sporadic) forms. Benign infantile familial convulsions (BIFC) is a recently recognized benign partial epilepsy syndrome. In the diagnostic scheme proposed by Engel (2001), BIFC is classified under familial autosomal dominant focal epilepsies. There are some clinical and EEG features that may potentially allow the differentiation of the two syndromes, even in the absence of family history (see differential diagnosis section below).

Epidemiology of BIFC

BIFC is rare; its prevalence is unknown. BIFC is more common in females, with a 2:1 ratio reported (Vigevano *et al.* 1994). In a series of 75 patients with afebrile infantile convulsions, 8 had partial seizures and a family history of afebrile infantile convulsions (Okumura *et al.* 1996).

Clinical manifestations of BIFC

The onset of BIFC is between 3.5-12 months of age, though onset at up to 20 months has been reported (Vigevano 2005). Seizures are partial at onset, and may or may not secondarily generalize. They typically occur in clusters of 5-10 a day (Duchowny and Harvey 1996; Vigevano

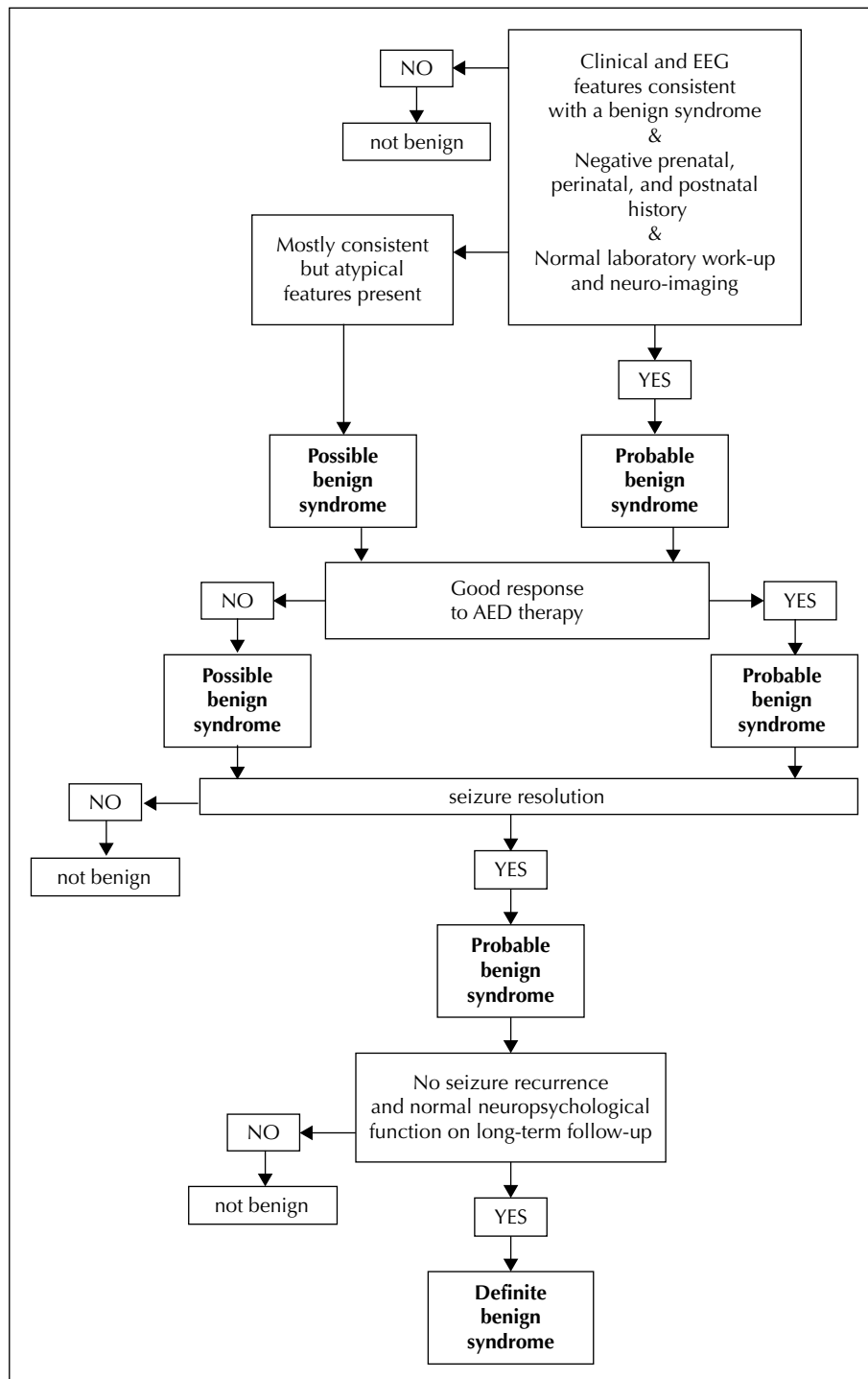


Figure 1. Proposed diagnostic algorithm for the diagnosis of benign epilepsy syndromes (see table 2 for definition of possible, probable, and definite).

et al. 1992). Seizures may also occur in wakefulness or drowsiness and are characterized by psychomotor arrest, eye deviation and head version to one side, diffuse hyper-tonia, cyanosis and unilateral limb jerks which then be-

come bilateral and may be synchronous or not (Vigevano *et al.* 1994, Malafosse *et al.* 1994). The direction of eye deviation and head version may differ from one seizure to the other in the same infant. Seizures last from one to

Table 2. Proposed definitions of *possible*, *probable*, and *definite* benign epilepsy syndromes.

Benign epilepsy syndrome	Definition
Possible	- clinical and EEG features consistent with a benign syndrome but there are one or more of the following atypical features (i) some atypical EEG findings (e.g. CSWSS during sleep) (ii) some atypical clinical features (e.g. impairment of neuropsychological function more than is expected in the typical course of the syndrome) or (iii) poor initial response to AED therapy
Probable	- clinical and EEG features consistent with a benign syndrome - negative prenatal, perinatal, and postnatal history - normal laboratory and neuroimaging - good response to AED therapy but follow-up is of limited duration (thus eventual complete response to therapy and resolution without sequelae have not yet been demonstrated)
Definite	- clinical and EEG features consistent with a benign syndrome - negative prenatal, perinatal, and postnatal history - normal laboratory and neuroimaging - good response to AED therapy and - seizure resolution with no seizure recurrence or neurologic sequelae after long-term follow-up and consistently normal neuropsychological function

several minutes; clusters of seizures last 1-3 days (Vigevano 2005).

EEG findings of BIFC

Interictal EEG is usually normal but may show spike slow-waves lateralized to the occipitoparietal areas. Should such spike slow-waves be present, they usually will cease to occur once the seizures are under control. Background EEG activity is normal (Vigevano *et al.* 1994).

Ictal EEG during BIFC seizures with secondary generalization is characterized by "recruiting rhythms" that start in the central-occipital areas on either side and spread to involve the entire brain (Vigevano *et al.* 1992; Malafosse *et al.* 1994) (*figure 2*). Ictal EEG discharges in eight patients with familial BIFC originated in the parietooccipital region in six patients and the temporal region in two (Lispi *et al.* 2001). Ictal EEG discharges in 15 patients with sporadic (non-familial) benign infantile convulsions originated in the temporal lobe in 10 patients and the parieto-occipital lobe in five (Lispi *et al.* 2001). The EEG region of onset may therefore be distinct for familial *versus* non-familial benign infantile convulsions, with the former more commonly beginning parietooccipital region and the latter mainly in the temporal region.

Diagnostic criteria of BIFC

The features most characteristic of BIFC, aiding in its diagnosis are: **(i)** family history of benign infantile seizures in familial forms **(ii)** normal premorbid development, **(iii)**

onset between 3-12 months of age, **(iv)** occurrence of partial seizures in clusters, **(v)** occipito-parietal localization of seizures, **(vi)** normal interictal EEG, **(vii)** normal psychomotor development **(viii)** good response to treatment (Vigevano 2005).

Differential diagnosis

Clinically, the familial and non-familial forms of benign infantile convulsions share several features including motor arrest, impairment of consciousness, staring, and occurrence of seizures in clusters (Caraballo *et al.* 2003, Vigevano 2005). While subtle clinical differences may exist, EEG better differentiates BIFC from BPEI-CPS and BPEI-SGS (*table 3*). In BIFC, seizure origin is most commonly parieto-occipital, and left-right side alternations may be seen whereas in BPEI-CPS, seizure origin is usually temporal and it is variable in the BPEI-SGS (Capovilla and Vigevano 2001). EEG can also distinguish BIFC from benign infantile focal epilepsy with midline spikes and wave during sleep (BIMSE) (see below).

Genetics of BIFC

Among family members of 17 patients with BIFC, 31 first or second degree relatives had a history of BIFC; four had other forms of epilepsy (Vigevano *et al.* 1994).

BIFC is believed to have a penetrance of 0.7. That BIFC is a separate, distinct entity from benign familial neonatal convulsions (BFNC) rather than late-onset BFNC is

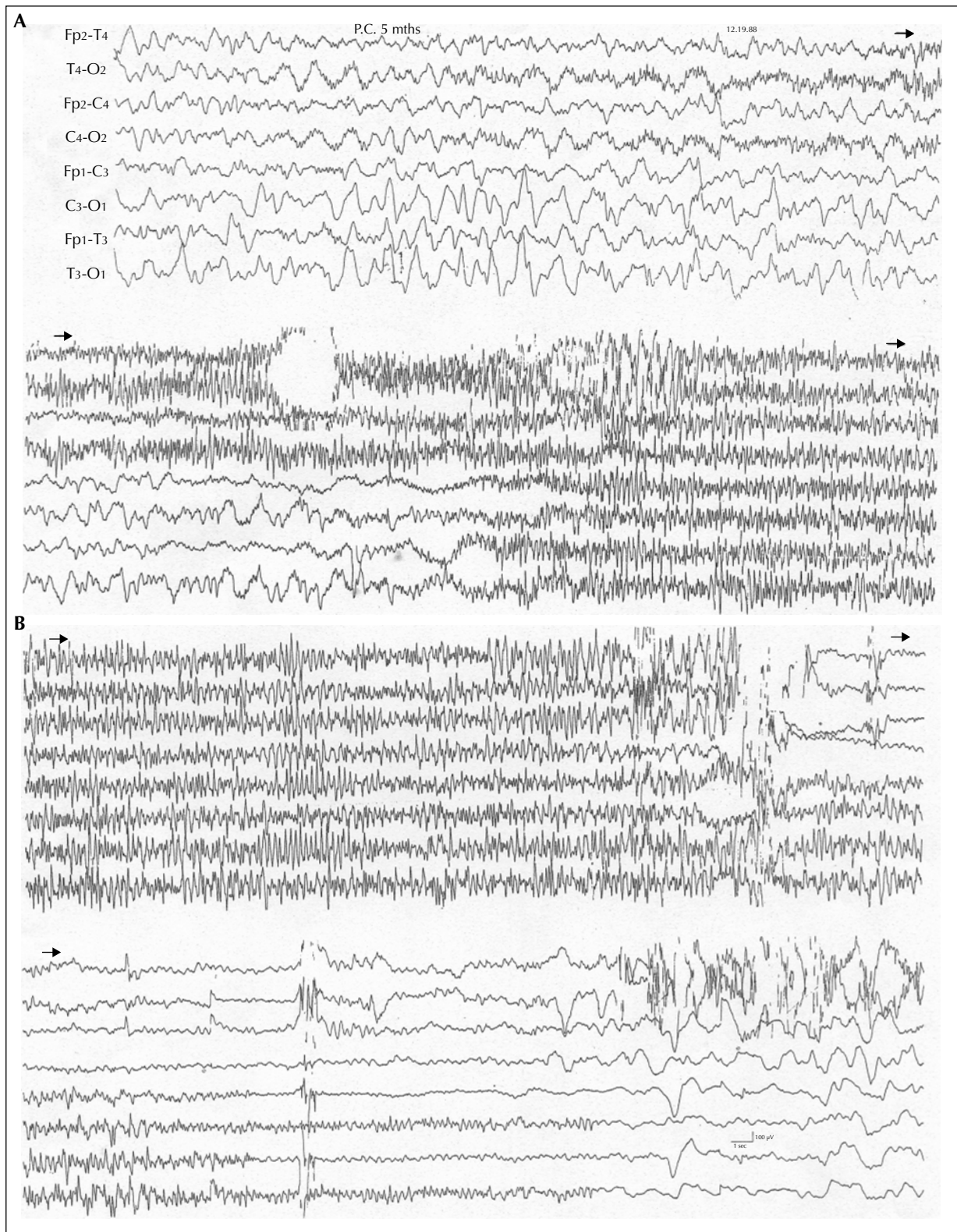


Figure 2. Ictal EEG recording of a nocturnal seizure in a child with BIFC showing an ictal recruiting rhythm beginning in the right occipital region, spreading to involve the central and temporal region, and finally the left hemisphere (A). Discharge cessation was asynchronous between the two sides (B). (Reproduced with kind permission of Springer Science and Business Media).

Table 3. Differential diagnosis of benign infantile localization-related epilepsies.

	Syndrome	Eponyms or suggested eponyms	Distinguishing clinical features	Distinguishing EEG features
Familial benign localization-related infantile convulsions	Benign infantile familial convulsions (BIFC)	Vigevano's syndrome	Presence of clear family history of benign infantile convulsions, autosomal dominant pattern of inheritance	Origin of ictal discharges most commonly parieto-occipital
	Familial infantile convulsions and choreoathetosis (ICCA)	Szepietowski's syndrome	Occurrence of BIFC and/or paroxysmal choreoathetosis in several members of the same family	No distinguishing features described
	Benign infantile familial convulsions/familial hemiplegic migraine (BIFC/FHM)	Terwindt's syndrome	Occurrence of FHM, BIFC, or both in members of the same family	No distinguishing features described
Sporadic benign localization-related infantile convulsions	Benign partial epilepsy of infancy with complex partial seizures (BPEI-CPS)	Watanabe's syndrome	-Despite possible presence of family history, no clear pattern of inheritance -Occurrence of limb or orofacial automatisms -Secondary generalization may occur, but not consistently during each seizure	Origin of ictal discharges is usually temporal
	Benign partial epilepsy of infancy with secondary generalized seizures (BPEI-SGS)	Watanabe-Okumura syndrome	Secondary generalization consistently occurs during each seizure	Variable origin of ictal discharges
	Benign infantile focal epilepsy with midline spikes and waves during sleep (BIMSE)	Bureau-Capovilla syndrome	Staring, psychomotor arrest, stiffening of the arms, loss of consciousness, and cyanosis (particularly of the face)	Sleep EEG shows diphasic spikes followed by a slow-wave originating in the vertex region
	Benign infantile convulsions associated with mild gastroenteritis	Morooka's syndrome	Afebrile seizures in an infant with mild diarrhea secondary to gastroenteritis without dehydration or major electrolyte abnormalities	Variable origin of ictal discharges

supported by failure to demonstrate linkage of BIFC to chromosome 20 (Malafose *et al.* 1994), for which there is an association with BFNC (Leppert *et al.* 1989).

The genetic heterogeneity of BIFC is evidenced by demonstration of linkage to chromosome 19q (Guipponi *et al.* 1997) as well as chromosome 2q24 (Malacarne *et al.* 2001). In addition, a misense mutation on chromosome 1 in the gene coding for a Na,K-ATPase protein, *ATP1A2*, has been identified in families in which there is the occurrence of familial hemiplegic migraine (FHM), BIFC, or both (Terwindt *et al.* 1997, Vanmolkot *et al.* 2003). Loss of function of this ATPase may lead to neuronal hyperexcitability and facilitation of cortical spreading depression, which has been implicated in the pathogenesis of migraine aura. The age-dependent differential expression of the $\alpha 2$ -isoform of this ATPase protein explain the different clinical effects of *ATP1A2* mutations in the very young (BIFC caused by neuronal hyperexcitability) *versus* in

adulthood (FHM caused by a reduced threshold for cortical spreading depolarization [Vanmolkot *et al.* 2003]). Heron *et al.* (2002) identified two families in whom all features of a benign epilepsy syndrome were present, but with seizure onset in the first month of life. They named this entity *benign familial neonatal-infantile seizures* (BFNIC). Genetic testing on members of these families identified mutations in voltage-gated potassium channel proteins, *KCNQ2* and *KCNQ3* (for which linkage has been established in BFNC [Lerche *et al.* 1999]) in one family and aminoacid changes in a subunit of the voltage-gated sodium (*SCN2A*) channel $\alpha 2$ -subunit on chromosome 2q24 in both families. The authors stated that "this discovery highlights the increasing complexity of phenotype-genotype correlations in epilepsy channelopathies; the same syndrome can be caused by mutations in different channel genes (*KCNQ2* and *KCNQ3*) and different mutations in the same gene can cause distinct phenotypes

(e.g. *SCN2A*)" (Heron *et al.* 2002). Mutations in subunits of *SCN2A* has also been associated with generalized epilepsy with febrile seizures plus (GEFS+) (Wallace *et al.* 1998, Baulac *et al.* 1999). Recently, a novel mutation in *SCNA2* was identified in a family with three individuals affected with BIFC over three generations (Striano *et al.* 2006).

Infantile convulsions and choreoathetosis (ICCA)

Szepetowski *et al.* (1997) identified four families in which family members had been diagnosed with either familial (autosomal dominant) BIFC or paroxysmal choreoathetosis, the latter being characterized by attacks of spontaneous or movement-induced choreoathetosis. In eight patients, both clinical manifestations were present. They thus defined a new syndrome: ICCA, an autosomal dominant disorder with a penetrance of approximately 0.8. They then demonstrated lack of linkage in all these ICCA family members to all regions in which genes have been mapped for BIFC and other paroxysmal choreoathetosis forms, even in family members manifesting only BIFC. Subsequently, linkage to chromosome 16p12-q12 was demonstrated in seven BIFC families in whom linkage to chromosome 19 had been excluded (Caraballo *et al.* 2001). None of these family members were affected with choreoathetosis. Similar results were found among 16 other families with BIFC (Weber *et al.* 2004). The authors suggested that different mutations in different genes located within this region on chromosome 16 may account for the distinct entities of certain epilepsy syndromes, choreoathetotic disorders, and combinations of the two, as in ICCA. It has also been hypothesized that "epileptic infantile seizures and [...] choreo-athetotic attacks are two different manifestations of the same neuronal membrane dysfunction in different territories, their respective occurrence depending on brain maturation" (Koch *et al.* 1999).

Management and prognosis of BIFC

For clearly familial forms of benign infantile convulsions, treatment may be withheld (Vigevano 2005). When treatment has been given, seizure control has been achieved with a variety of drugs including carbamazepine, phenobarbital, valproate, or zonisamide. In Vigevano's original series of five infants with seizure onset between the ages of 4-7 months (Vigevano *et al.* 1992), treatment was initiated in the cases in which seizures occurred in clusters. All seizures remitted within 24-48 hours. Continuous daily treatment was administered for 1-2 years, and follow-up of these patients for 4-5 years revealed no seizure recurrence and normal psychomotor development (Vigevano *et al.* 1994). In a series of 17 patients with BIFC followed from 2-11 years, no children had seizure recurrence and EEG normalized in all cases. In 16 patients, psychomotor development was normal; one patient had mild mental retardation (Vigevano *et al.* 1994).

Sporadic benign localization-related epilepsy syndromes of infancy

The recognition of sporadic forms of benign infantile convulsions has led to the definition of two types of non-familial benign partial epilepsy of infancy (BPEI): *benign partial epilepsy with complex partial seizures* (BPEI-CPS) and *benign partial epilepsy with secondarily generalized seizures* (BPEI-SGS). In the diagnostic scheme proposed for epilepsy syndromes (Engel 2001), sporadic BPEI is classified under the idiopathic focal epilepsies.

Epidemiology of BPEI

Data on the prevalence of BPEI is scarce. In a study of 75 patients in Japan with seizure onset in the first two years of life, 22 (29 %) of patients were found to have BPEI, 14 of which were sporadic cases (Okumura *et al.* 1996). Of the 22 cases, eight had CPS only, ten had a combination of CPS with or without secondary generalization, and four had CPS which consistently secondarily generalized.

Clinical manifestations of BPEI

The age of onset of BPEI was initially considered to be strictly in the first year of life (Capovilla and Vigevano 2001, Watanabe *et al.* 1990). However, BPEI-CPS has been reported to begin between the ages of 3-20 months, with a median age of onset of 9.5 months (Capovilla *et al.* 1998, Watanabe *et al.* 1987, Watanabe *et al.* 1990). Seizures occur more frequently in wakefulness than in sleep, but may occur in either.

Seizures in BPEI-CPS are characterized by some combination of staring, loss of consciousness, cyanosis (particularly of the face), and psychomotor arrest. Subtle convulsive movements may also occur. These include simple movements of the head or extremities, mild clonic movements of the face, eyelids, or limbs, increased limb tone, automatisms, and head and eye version (Capovilla and Vigevano 2001, Okumura *et al.* 2000, Watanabe *et al.* 1987). Seizures may or may not secondarily generalize. They may vary from one episode to the other in the same infant (Capovilla and Vigevano 2001). Seizures always occur in clusters and may occur from once to several times a day (Watanabe *et al.* 1987, Watanabe *et al.* 1990). While in some reports seizure frequency was only 3-4 times per year (Capovilla and Beccaria 2000), in other reports clusters recurring at 1-8 week intervals were described (Capovilla and Vigevano 2001, Capovilla *et al.* 1998, Watanabe *et al.* 1987). The duration of seizures ranges from 40 seconds to 5 minutes, and seizures are often followed by post-ictal sleep, but not by post-ictal deficits (Capovilla and Beccaria 2000). Status epilepticus has not been reported in this syndrome.

Seizures in BPEI-SGS are complex partial seizures that always and promptly are followed by secondary generalization. The clinical manifestations of BPEI-SGS are very

similar to those of BPEI-CPS. Thus, BPEI-SGS may be misdiagnosed as BPEI-CPS (Watanabe *et al.* 1993). The main distinguishing feature is that the seizures of BPEI-SGS consistently secondarily generalize during each seizure whereas secondarily generalization may, but does not necessarily, occur in BPEI-CPS (Capovilla and Vigeveno 2001).

EEG findings of BPEI

The interictal EEG in BPEI-CPS and BPEI-SGS is normal in wakefulness and sleep (Capovilla *et al.* 1998, Capovilla and Vigeveno 2001, Capovilla and Beccaria 2000, Watanabe *et al.* 1987).

In BPEI-CPS, ictal EEG exhibits low-voltage fast focal discharges or repetitive sharp alpha or theta waves that progressively decrease in frequency and increase in amplitude. These are followed by theta and delta waves intermixed with spikes or sharp waves that may or may not gradually or rapidly spread to adjacent regions or, in the case of temporal origin, to the contralateral temporal area (*figure 3*). The origin of ictal discharges in BPEI-CPS can vary, and may occur in the central, frontal, or parietal areas, but most commonly occurs in temporal or occipital regions (Capovilla *et al.* 1998, Capovilla and Vigeveno 2001, Watanabe *et al.* 1987, Watanabe *et al.* 1990).

In BPEI-SGS, ictal EEG shows focal discharges, fast waves of low-voltage, or rhythmic or repetitive sharp waves or spikes which progressively increase in amplitude and decrease in frequency, spreading to contralateral and adjacent regions. These epileptic discharges bare resemblance to epileptic recruiting rhythm, and later become mixed with slow waves that progressively decrease in frequency, yielding spikes, polyspikes, or sharp-wave

complexes. These discharges show less bilateral synchrony and are accompanied by less clonic seizure activity in comparison to those seen in older children and adults (Watanabe *et al.* 1993).

The localization of ictal discharges in BPEI-SGS varies, including parietal, or occipital origin, but most commonly central. This is considered to be one of features distinguishing BPEI-SGS from BPEI-CPS. Origin of ictal discharges may alternate from one side to the other during different seizure episodes in the same patient (Capovilla and Vigeveno 2001, Watanabe *et al.* 1993).

Diagnostic criteria of BPEI

The following diagnostic criteria have been proposed for BPEI-CPS: **(i)** a family history of benign seizures, **(ii)** normal psychomotor development and neurologic exam prior to seizure onset, **(iii)** seizure onset between 3-10 months of age with no seizures occurring in the neonatal period, **(iv)** complex partial seizures occurring in clusters **(v)** normal interictal EEG, and **(vi)** good response to treatment (Watanabe *et al.* 1990; Watanabe *et al.* 1987). Some have suggested that the diagnosis can not be definitively made until adolescence or even adulthood when psychomotor development can be assessed as completely normal and there has been a long seizure-free period (Okumura *et al.* 2000, Watanabe *et al.* 1990, Watanabe and Okumura 2000). Okumura *et al.* (2000) believe the diagnosis can be made only when seizures do not occur beyond two years of age.

The diagnostic criteria for BPEI-SGS include **(i)** normal psychomotor development prior to onset, **(ii)** no underlying neurological disorders, **(iii)** onset between 3-20 months

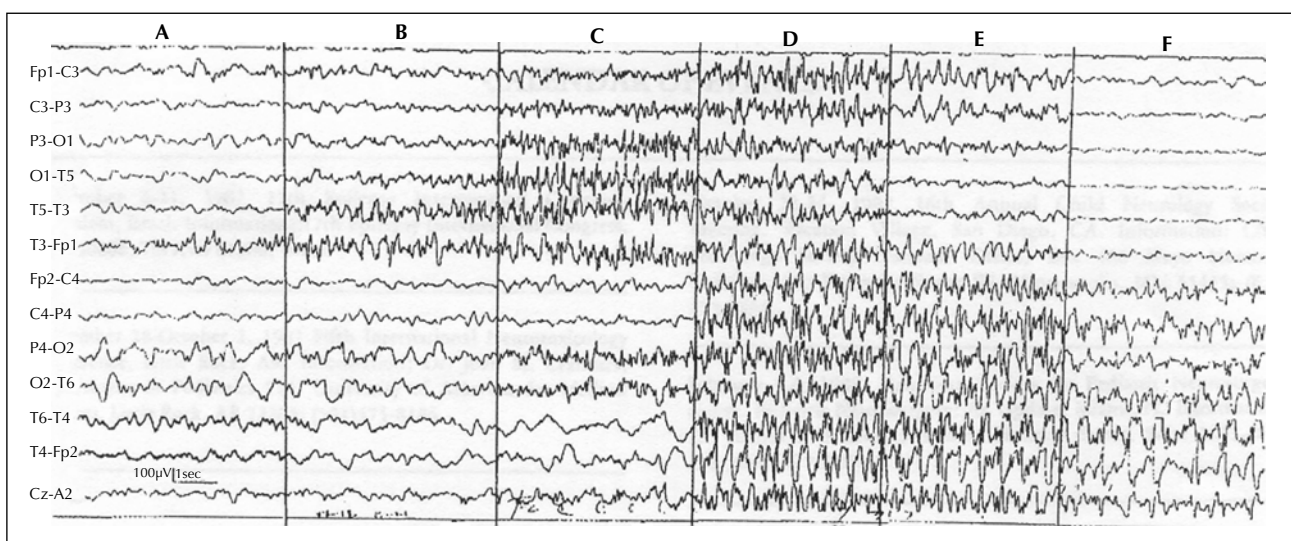


Figure 3. Ictal EEG recording of seizure in a child with BPEI-CPS showing initial discharges beginning in the left temporal area with spread to adjacent unilateral regions. (Reprinted from *Pediatric Neurology*. Volume 3. Watanabe K, Yamamoto N, Negoro T, Takaesu E, Aso K, Furune S, Takahashi I. Benign Complex Partial Epilepsies of Infancy. Pages 208-211. 1987, with permission of Elsevier).

of age (**iv**) partial seizures consisting of motionless stare or blank eyes, often occurring in clusters (**v**) prompt and consistent secondary generalization (**vi**) normal Interictal EEG, and (**vii**) good response to treatment (Watanabe and Okumura 2000).

Differential diagnosis

BPEI-SGS may be distinguished from primary generalized tonic or tonic-clonic seizures by the presence of an initial partial phase, though this is often clinically difficult to appreciate, and EEG is necessary for confirmation (Okumura *et al.* 1996).

BPEI must be distinguished from BIFC though these syndromes have been considered to overlap (Caraballo *et al.* 2003, Okumura *et al.* 1996). It has been suggested that specific to BPEI-CPS as compared to BIFC is the occurrence of limb or orofacial automatisms (Watanabe *et al.* 1990). Differentiation of BIFC from BPEI-SGS based on electro-clinical features is challenging; a family history of afebrile infantile convulsions is distinctly absent among patients with BPEI-SGS, and origin of ictal EEG discharges is more variable than in BIFC (*table 3*).

BPEI may be distinguished from benign infantile epilepsy with midline SW during sleep (BIMSE) in that the latter starts earlier, has a higher seizure frequency, and seizures consist of more lateralizing signs and automatisms. In addition, cyanosis is common in BIMSE and rare in BPEI. Moreover, the EEG in BPEI is normal in wakefulness and sleep, unlike in BIMSE (see below) (Capovilla and Beccaria 2000, Capovilla *et al.* 2006).

Genetics of BPEI

While a family history of febrile and afebrile seizures and even BIFC is often present among patients with BPEI-CPS, in up to 50% of patients (Watanabe *et al.* 1987, Capovilla *et al.* 1998, Capovilla and Vigeveno 2001), genetic studies on this syndrome are scarce. A family history of seizures is absent in BPEI-SGS (Capovilla and Vigeveno 2001).

Management and prognosis of BPEI

Seizures have been reported to cease at between 2.3 to 3.6 years of age (Capovilla and Beccaria 2000). In the initial description of BPEI it was proposed that treatment with carbamazepine or phenobarbital results in good control (Watanabe *et al.* 1987). While no controlled studies have been conducted, a small retrospective study suggests carbamazepine may be more effective than phenobarbital or diazepam (Yanagihara *et al.* 2003). However, treatment may not be necessary for BPEI (Okumura *et al.* 2000, Takeuchi *et al.* 1998).

As a rule, following resolution of BPEI seizures, subsequent seizures do not occur and psychomotor development is normal, as is consistent with the definition of a benign syndrome (Capovilla and Vigeveno 2001, Watanabe *et al.* 1990).

On long-term follow-up, the diagnosis in a small minority of patients will be changed based on the occurrence of subsequent seizures or developmental delay (Okumura *et al.* 2006). Among 39 patients diagnosed with possible BPEI followed up beyond eight years of age, three patients had a recurrence of unprovoked seizures at age two years. One patient's seizures occurred 12 years after cessation of BPEI seizures; MRI revealed an AVM. Four of the 39 patients had cognitive problems at long-term follow-up. Paroxysmal kinesigenic choreoathetosis occurred in three patients starting at age 6-8; these are a distinct group of patients from those with familial infantile convulsions and choreoathetosis (ICCA) described by Szeppetowski *et al.* (1997). Nine percent of patients with BPEI later had convulsions associated with mild gastroenteritis at 22 months of age (Okumura *et al.* 2006a).

Other benign localization-related infantile epilepsy syndromes

Benign infantile convulsions associated with mild gastroenteritis

In this entity, first described in Japan by Morooka (1982), there is the occurrence of afebrile seizures in an infant with mild diarrhea secondary to gastroenteritis without dehydration or major electrolyte abnormalities (Capovilla and Vigeveno 2001; Komori *et al.* 1995). Of 342 patients with gastroenteritis, 3 % were diagnosed with this entity. While it was initially considered a partial epilepsy syndrome, primary generalized cases have been described (Capovilla and Vigeveno 2001). Family history is typically negative for seizures or epilepsy (Komori *et al.* 1995). Afebrile convulsions usually occur in 1% of children with viral gastroenteritis (Capovilla and Vigeveno 2001). Rotavirus and less commonly Norwalk virus may be causative agents of the gastroenteritis (Komori *et al.* 1995, Capovilla and Vigeveno 2001).

Benign convulsions associated with mild gastroenteritis begins between four months to three years of age in a previously healthy child (Komori *et al.* 1995). Seizures typically begin during the first five days of an illness characterized by mild gastroenteritis, though onset of seizure prior to the diarrhea may occur in up to 40 % (Komori *et al.* 1995). Cases of simple partial tonic-clonic seizures, complex partial seizures with secondary generalization, or primary GTCS have been reported as part of this syndrome (Komori *et al.* 1995, Imai *et al.* 1999). Seizures may occur in clusters or as single or a few isolated episodes. Seizures typically last no longer than five minutes though they have lasted for up to 20 minutes in some cases (Komori *et al.* 1995). While some have considered benign convulsions occurring in the setting of a mild gastroenteritis to be situation-related seizures (Okumura *et al.* 2006b), the designation of this symptom complex as an epilepsy syndrome is based on the usual occurrence of more than

one seizure within a defined age group, with a well defined prognosis (Capovilla and Vigeveno 2001, Komori *et al.* 1995). We tend to favor the first designation.

Interictal EEG is normal. EEG recordings of three seizures revealed an initial fast rhythm of low amplitude recruiting rhythm from the right occipital region in one seizure, from the right centroparietal region in another seizure, and from the left occipital area in a third (Imai *et al.* 1999). Despite the variation in site of origin of ictal discharges and in the initial 10 seconds of the clinical seizures, seizures were otherwise clinically identical.

It is recommended that stool rotavirus antigen detection, lumbar puncture, serum electrolytes, and EEG be obtained to rule out more serious illnesses (Komori *et al.* 1995).

This entity must be differentiated from Reye syndrome, encephalitis, meningitis, and other benign infantile epilepsy syndromes. The presence of a mild gastroenteritis and the temporal association of seizure onset combined with the absence of serum and CSF biochemical abnormalities allows for this.

Diazepam has been used successfully in the acute treatment of this entity; further therapy following symptom resolution is considered unnecessary. Once the seizures associated with mild gastroenteritis cease, recurrence of seizures is rare and in no case has there been a subsequent diagnosis of epilepsy (Komori *et al.* 1995, Imai *et al.* 1999).

Benign infantile focal epilepsy with midline spikes and waves during sleep

This syndrome was first described by Bureau and Maton (1988) and later refined by Capovilla and Beccaria (2000). Capovilla and Beccaria (2000) identified 12 cases of partial epilepsy occurring in children aged 1-2.5 years who had normal development, negative laboratory and neuroimaging studies and who shared several electroclinical features.

Seizures occurred in wakefulness or sleep, with onset characterized by some combination of staring, psychomotor arrest, stiffening of the arms, and loss of consciousness, and, in all, cyanosis, particularly of the face. Seizure duration ranged from 1-5 minutes. Seizures ceased between approximately 2.3 to 3.6 years of age.

EEG during wakefulness consistently showed no abnormalities. EEG during sleep, however showed typical findings consisting of diphasic spikes of low or medium voltage followed by a bell-shaped slow-wave of higher voltage than the spikes. These abnormalities began in stage I of sleep, increased in frequency in stage II, then decreased during slow-wave sleep. Spikes and waves occurred either singly or in groups in short series and originated in the vertex region, with occasional spread to central areas. Morphologically, they were readily discernible from physiological sleep vertex spikes. These EEG findings were present at clinical onset of seizures and persisted for 6 months to 2.5 years after cessation of

clinical seizures. Thereafter, they completely disappeared in all cases with more than a two year follow-up. AED therapy is considered unnecessary considering the relatively low seizure frequency and short duration of the syndrome (Capovilla and Vigeveno 2001).

Genetics of the partial epilepsy syndromes

In recent years, several epilepsy syndromes occurring in various age groups have been shown to be associated with specific gene mutations (Bate and Gardiner 1999, Mikati and Rahi 2003). An overview of the mutations causing the partial epilepsy syndromes in both childhood and adulthood is presented in *table 4*. The table illustrates that mutations in the same gene may lead to different epilepsy syndromes, and on the other hand, mutations in different genes may lead to the same epilepsy syndrome.

As mentioned above, BIFC has been linked to chromosome 19q (Guipponi *et al.* 1997) and chromosome 2q24 (Malacarne *et al.* 2001). In families with FHM, BIFC, or both, a mutation in chromosome 1 has been identified. (Terwindt *et al.* 1997, Vanmolkot *et al.* 2003). In addition, linkage to chromosome 16p12-q12 in ICCA patients has been demonstrated (Caraballo *et al.* 2001). Some of the genetic epilepsy syndromes may initially present as febrile seizures (Mikati and Rahi 2003).

The clinical implications of single gene mutations leading to partial epilepsy syndromes raises the possibility of targeted therapy. One example of such an approach is the development of targeted therapy for benign familial neonatal convulsions (BFNC). BFNC is an idiopathic epilepsy initially regarded as a generalized epilepsy, though partial onset has been described. It manifests on days 2-3 of life. BFNC exhibits autosomal dominant inheritance with a penetrance estimated at 0.85 (Charlier *et al.* 1998, Leppert *et al.* 1989, Lerche *et al.* 1999). Two genes have been linked to BFNC: EBN1 on chromosome 20q and EBN2 on chromosome 8q. The gene on chromosome 20 implicated in BFNC has been identified as *KCNQ2*, which encodes a delayed-rectified voltage-gated potassium channel (Lerche *et al.* 1999, Singh *et al.* 1998). A reduction in the potassium current through this channel leads to membrane hyperexcitability, which may explain the pathogenesis of the seizures in BFNC (Lerche *et al.* 1999) and raises the possibility of targeted therapy. A missense mutation in another voltage-gated potassium channel, *KCNQ3*, has been mapped to chromosome 8q24. This mutation alters the channel architecture, thus impairing the M-current (Hirose *et al.* 2000). Linkage to chromosome 8q24 has also been demonstrated in patients with a sub-syndrome of childhood absence epilepsy (Fong *et al.* 1998). Retigabine, a derivative of the nonopioid analgesic flupirtine that is still under study, has been shown to increase opening of potassium channels formed by *KCNQ2* and *KCNQ3* sub-

Table 4. Genetics of the partial epilepsy syndromes in infants, children, and adults.

Syndrome	Mode of inheritance	Chromosome	Gene/Gene product	References
Benign infantile familial convulsions	autosomal dominant	chromosome 19q chromosome 2q	Unknown SCN2A: voltage-gated sodium channel α 2-subunit,	Striano <i>et al.</i> 2006, Guipponi <i>et al.</i> 1997, Malacarne <i>et al.</i> 2001
Familial hemiplegic migraine/BIFC	autosomal dominant	chromosome 1	ATP1A2A, Na,K-ATPase protein	Terwindt <i>et al.</i> 1997, Vanmolkot <i>et al.</i> 2003
Familial infantile convulsions and choreoathetosis	autosomal dominant	chromosome 16p12-q12	Unknown	Szepetowski <i>et al.</i> 1997, Caraballo <i>et al.</i> 2001, Weber <i>et al.</i> 2004
Benign familial neonatal-infantile seizures	autosomal dominant	chromosome 20 chromosome 8q24 chromosome 2q24	KCNQ2 and KCNQ3, voltage-gated potassium channel proteins SCN2A, a voltage-gated sodium channel α 2-subunit	Heron <i>et al.</i> 2002, Lerche <i>et al.</i> 1999
Autosomal dominant nocturnal frontal lobe epilepsy	autosomal dominant	chromosome 20q13.2 chromosome 1q chromosome 15q24 chromosome 3p22-p24 and chromosome 8q11.2-q21.1	CHRNA4, α 4-subunit of the neuronal nicotinic acetylcholine receptor CHRNA2, β 2-subunit of the neuronal nicotinic acetylcholine receptor Unknown	Steinlein <i>et al.</i> 1995, Phillips <i>et al.</i> 2000, De Fusco <i>et al.</i> 2000, Hirose <i>et al.</i> 1999, Schaffer <i>et al.</i> 1994, Combi <i>et al.</i> 2005
Familial partial epilepsy with variable foci	autosomal dominant	chromosome 22q11-q12 ? chromosome 2	Unknown	Scheffer <i>et al.</i> 1998, Xiong <i>et al.</i> 1999
Familial lateral temporal lobe epilepsy	autosomal dominant	chromosome 10q24	LG11, leucine-rich glioma-inactivated-1 gene	Ottman <i>et al.</i> 1995, Kalachikov <i>et al.</i> 2002, Berkovic <i>et al.</i> 2004
Benign childhood epilepsy with centrotemporal spikes	EEG: autosomal dominant. Clinical: multi-factorial	chromosome 15q14	Unknown ? alpha 7 subunit of the acetylcholine receptor	Bray and Wisner 1964, Neubauer <i>et al.</i> 1998
Autosomal rolandic epilepsy with paroxysmal exercise induced dyskinesia and writer's cramp	autosomal recessive	chromosome 16p12-q12	Unknown	Guerrini <i>et al.</i> 1999
Autosomal dominant rolandic epilepsy with sleep dyspraxia	autosomal dominant with clinical anticipation	unknown	Unknown. Possibly due to expansion of trinucleotide repeats	Scheffer <i>et al.</i> 1995

units, both of which have been shown to be abnormal in BNFC (Cooper 2001). Similar approaches may be possible for epilepsy syndromes in other age groups. In addition to the possibility of targeted drug therapy, it is hoped that

understanding the genetic mechanisms responsible for the various monogenic epilepsy syndromes will contribute to the understanding of the pharmacology of intractable epilepsy (Cossette and Rouleau 2006). □

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