

Benign pediatric localization-related epilepsies

Part II. Syndromes in childhood

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ABSTRACT – By definition, benign epilepsy syndromes occur in patients with no significant prenatal, perinatal, or postnatal complications, normal psychomotor development and negative laboratory and neuroimaging work-up, respond well to therapy, and remit without sequelae. The benign localization-related epilepsy syndromes of childhood include benign childhood epilepsy with centrotemporal spikes, Panayiotopoulos syndrome and Gastaut-type idiopathic childhood epilepsy with occipital paroxysms. Some patients initially presumed to have these or, for that matter, other benign syndromes in other age groups, follow a less typical course and continue to experience seizures or to exhibit neuropsychological deficits. Thus the diagnosis of a “possible” or “probable” benign epilepsy syndrome may need to be applied to patients initially suspected of having such syndromes until follow-up shows that they clearly follow a benign course. In Part I (Chahine and Mikati 2006) of our two-part review article, we discussed benign localization-related syndromes encountered in infancy. In this second part, we review the epidemiology, clinical manifestations, neuropsychological features, EEG findings, work-up and diagnostic criteria, differential diagnosis, genetics, management and prognosis of the three childhood-onset syndromes. In addition, we discuss their occasional overlap with or progression into other syndromes.

Key words: benign localization-related epilepsy syndrome, rolandic epilepsy, Panayiotopoulos syndrome, Gastaut-type occipital epilepsy

In this second part of our two-part review (Chahine and Mikati 2006) of the pediatric benign localization-related epilepsy syndromes, the benign localization-related epilepsy syndromes of childhood are reviewed (see *table 1* for abbreviations).

drome among school-aged children (Ericksson and Koivikko, 1997, Sindevall *et al.* 1993). It accounts for up to 23% of new-onset childhood epilepsy disorders (Wirrell 1998) and has a male predominance (Beaussart, 1972, Ma and Chan, 2003).

Benign childhood epilepsy with centrotemporal spikes (BECTS)

Epidemiology

BECTS is the most common localization-related epilepsy syn-

Clinical manifestations

Onset of BECTS occurs between the age of three and 13 years, with a peak incidence around 8-9 years (Kramer *et al.* 2002, Beaussart, 1972). A history of febrile convulsions, particularly complex febrile convulsions, is

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present in up to 16% and a history of neonatal and infantile seizures in 1%-8% of cases (Wirrell, 1998, Beaussart, 1972, Ma and Chan, 2003).

Typical clinical manifestations of BECTS

The majority of seizures are nocturnal, occurring shortly after sleep-onset or before awakening in 65% of patients, although strictly diurnal seizures or both nocturnal and diurnal seizures may also occur (Wirrell, 1998, Manelis and Dublin, 1995, Beaussart, 1972).

Seizures are somatosensory at onset, with symptoms including unilateral tongue, gum, lips, or inner cheek paresthesias, jaw and tongue stiffness or a sensation of choking. Less commonly, jerking or paresthesias of a limb, usually the arm, loss of vision, abdominal pain, or vertigo are reported (Manelis and Dublin, 1995, Wirrell, 1998). In 12% of the patients, this may be the sole manifestation of the seizure (Ma and Chan, 2003). In 34%, it is followed by unilateral or generalized convulsions that are either tonic, clonic, or tonic-clonic, most commonly involving the face, lips, tongue, or muscles of the pharynx and larynx (Ma and Chan, 2003, Manelis and Dublin, 1995, Lerman and Kivity, 1975, Holmes, 1993), the latter leading to speech arrest or anarthria and excessive drooling. A combination of different seizure types may occur in the same child (Kramer *et al.* 2002). Occasionally, partial motor seizures may change from one side of the body to the other without secondary generalization (Wirrell, 1998). In up to 54%, generalized seizures without a clinically apparent focal onset may occur (Ma and Chan, 2003).

BECTS seizures have been categorized into three types:

- i) hemifacial seizures with anarthria and drooling, with preservation of consciousness,
- ii) as described in (i) but with alteration of consciousness, often accompanied by gurgling noises or grunting,
- iii) with secondarily generalized tonic-clonic seizures (Wirrell, 1998, Manelis and Dublin, 1995, Beaussart, 1972).

Seizures typically last seconds to minutes. Seizure frequency varies: 10-13% of patients will have only one

seizure, 70% have seizure recurrences at 2-12 month intervals, and 20% have daily seizures (Manelis and Dublin, 1995, Wirrell, 1998). In 62% of cases, 2-5 seizures will occur. Seizure onset prior to the age of three may predict the likelihood of multiple seizures (Kramer *et al.* 2002, Bouma *et al.* 1997).

Atypical clinical manifestations of BECTS

Atypical features are relatively common, occurring in up to 50% of patients. They may be more common among those with seizure-onset before 6 years of age. Developmental delay and diurnal-only seizures predict the occurrence of other atypical clinical features (Wirrell *et al.* 1995).

Atypical features include leg jerking, lateral body torsion, unilateral body sensations, epigastric pain, ictal blindness, status epilepticus, diurnal-only seizures, developmental delay, Todd's paresis, and an attention deficit disorder (Wirrell *et al.* 1995, Vinayan *et al.* 2005, Manelis and Dublin, 1995).

Partial status epilepticus occurs in up to 17% of cases of BECTS (Wirrell, 1998). The clinical picture includes slurred speech, constant drooling, oromotor dyspraxia, atonic nodding of the head, or facial myoclonias. These symptoms have been likened to those seen in opercular syndromes, in which bilateral opercular lesions or, in this case, ongoing seizure activity, are associated with loss of voluntary control of facial, pharyngeal, lingual, masticatory, and sometimes ocular muscles, while reflex and automatic function of these muscles remains intact (Gregory *et al.* 2002, Kramer *et al.* 2001, Saint-Martin *et al.* 1999, 2001a). This clinical picture correlates with the presence of continuous spike-waves during slow sleep (Fejerman *et al.* 2000).

Neuropsychological features of BECTS

Between 28% (Massa *et al.* 2001) and 53% (Vinayan *et al.* 2005) of children with BECTS display neuropsychological abnormalities during the active phase of the syndrome including cognitive dysfunction, with difficulties on

Table 1. Abbreviations used.

ABFCE	Atypical benign focal childhood epilepsy (pseudo Lennox-Gastaut syndrome)
BCEOP	Benign childhood epilepsy with occipital paroxysms
BECTS	Benign childhood epilepsy with centrottemporal spikes
CT	Centrottemporal
CSWSS	The EEG finding of continuous spike-waves during slow-wave sleep
ECSWSS	Epilepsy with continuous spike-waves during slow-wave sleep
IEDs	Interictal discharges
LKS	Landau-Kleffner syndrome

auditory-verbal and visuospatial memory and executive function tasks, language impairment, attention disorders, learning disabilities, and behavioral disturbances (Pinton *et al.* 2005, Sart *et al.* 2006, Croona *et al.* 1999, Saint-Martin *et al.* 1999, Ong and Wyllie, 2000, Wirrell, 1998; Vinayan *et al.* 2005, Deonna *et al.* 2000). The types of cognitive deficits correlate with the side of the centrotemporal (CT) abnormalities (Wirrell, 1998). For example, right hemisphere foci may interfere with visuospatial processing (Pinton *et al.* 2005, Piccirilli *et al.* 1994). Cognitive deficits are more likely to occur when interictal abnormalities are bilateral (Massa *et al.* 2001). A spike frequency of > 10/minute may be more likely to lead to language delay and cognitive/behavioral problems. Also, atypical seizure semiology often correlates with language dysfunction (Baglietto *et al.* 2001, Vinayan *et al.* 2005, Nicolai *et al.* 2006).

EEG findings in BECTS

Although mild background slowing is occasionally noted, EEG background activity is usually normal in BECTS. Interictal EEG shows high-voltage, diphasic or negative spikes, followed by prominent slow waves of less amplitude at the midtemporal (T3, T4) and central (rolandic) regions (C3, C4) (Wirrell, 1998, Minami *et al.* 1996, Holmes, 1993, Beaussart, 1972). Spike frequency varies

from one patient to another, and may vary in the same patient from one EEG to another (Holmes, 1993). Spikes occur individually or in clusters. Horizontal dipoles are common, with maximal negativity in the centrotemporal area and positivity in frontal regions (Kamada *et al.* 1998, Gregory and Wong, 1992) (*figure 1*). Marked activation of spikes occurs characteristically during drowsiness and sleep (Wirrell, 1998). The focus is unilateral in 55%-70% of cases and bilateral in 42% (Drury and Beydoun, 1991). When bilateral, they are either synchronous or more commonly asynchronous in terms of both the rate of firing and amplitude (Lerman and Kivity, 1975, Beaussart, 1972). Spikes are typically present in both central and temporal regions, but may shift location (Beaussart, 1972, Drury and Beydoun, 1991) or may occur exclusively in midtemporal or central regions (Holmes, 1993). Atypical spike locations occur in 17%-21% of patients. Many children who initially have occipital spikes are later found to have centrotemporal spikes (Wirrell, 1998, Holmes, 1993, Drury and Beydoun, 1991). There is a poor correlation between EEG findings and the clinical picture (Holmes, 1993). Voluntary tongue or mouth movements, or contralateral hand or finger movements have been shown to inhibit centrotemporal spikes (Gregory *et al.* 2002, Colamaria *et al.* 1991). The presence of dipole centrotemporal spikes implies a better prognosis, and lesser risk of

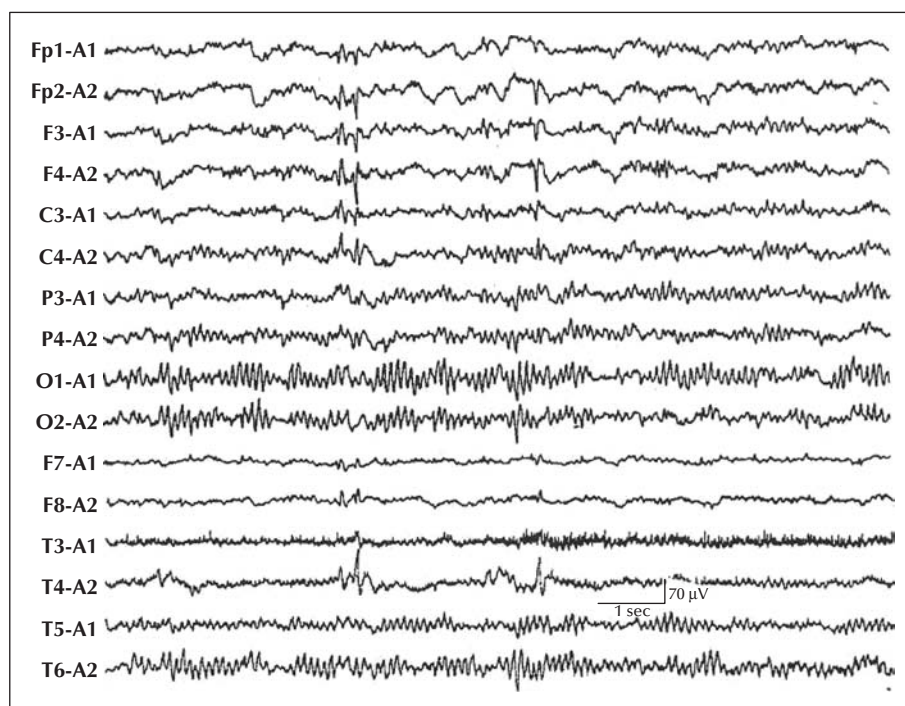


Figure 1. Interictal EEG in a child with BECTS showing a horizontal dipole: the sharp waves are of negative polarity in the right central and midtemporal regions and positive in the frontal regions (reproduced with kind permission of Blackwell Publishing from Drury I. EEG in benign and malignant epileptic syndromes of childhood. *Epilepsia* 2002; 43 (Suppl. 3): 17-26).

seizures, developmental delay, abnormalities on neurological examination, and of academic difficulties (Gregory and Wong, 1992). Six interictal EEG patterns have been shown to correlate with atypical BECTS: intermittent slow-wave foci, multiple asynchronous spike-wave foci, long clusters of spike-waves, generalized 3 Hz/second spike-wave discharges, conjunction of interictal discharges with negative or positive myoclonias, and an abundance of interictal abnormalities during both wakefulness and sleep. The occurrence of three of these six patterns was suggested to be predictive of those BECTS patients at higher risk of poor academic performance, inattention, impulsivity, decreased short-term memory, and other neuropsychological deficits (Massa *et al.* 2001). Generalized 3Hz spike-wave discharges and absence seizures may also occur in BECTS patients, although this is rare (Gelisse *et al.* 1999).

Centro-temporal spikes, or rolandic spikes, are a common finding and only 5% of these children will manifest BECTS (Wirrell, 1998). Up to 5.6% of ADHD patients exhibit centrotemporal spikes on EEG (Holtmann *et al.* 2003) and central spikes with a BECTS-like morphology are seen in a number of clinical syndromes besides BECTS (Holmes, 1993, Manelis and Dublin, 1995).

Ictal EEG recordings during a nocturnal seizure in a child in stage II sleep initially showed low-voltage, fast activity originating in the centrottemporal area unilaterally and spreading over the entire ipsilateral then contralateral hemisphere (Dalla-Bernardina and Tassinari, 1975). Ictal EEG recordings of a diurnal seizure showed focal decrimental activity in the centrottemporal region followed by dense spikes in the same location. Seizure activity did not spread to adjacent brain areas and there was no postictal slowing (Wirrell, 1998).

Interictal EEG and magnetoencephalographic (MEG) analysis studies have shown the epileptogenic focus of BECTS to be localized to the radial somatosensory cortex (Minami *et al.* 1996), in the inferior rolandic (face) or superior rolandic (hand) regions (Kamada *et al.* 1998).

Work-up and diagnostic criteria

In one report, BECTS was misdiagnosed in 84% of cases by a general pediatrician (Ma and Chan, 2003). Considering the benignity of BECTS, correct diagnosis is essential. A sleep EEG is necessary, particularly if the awake EEG shows no abnormalities (Panayiotopoulos, 1993). Typical EEG findings, accompanied by a typical clinical history and negative neurological examination, are generally considered sufficient to make the diagnosis of BECTS (Wirrell, 1998).

The diagnostic criteria of BECTS include: i) brief, stereotypical, simple partial, unilateral facial motor seizures associated with somatosensory symptoms, and a tendency for secondary generalization, commonly occurring in sleep; ii) seizure-onset between the ages of 3-13; iii) spontaneous recovery before the age of 16; iv) absence of

anatomic CNS lesions that could be related to the epilepsy; and v) no history or current neurological or intellectual deficit (Engel 2001, Commission on Classification and Terminology of the International League Against epilepsy 1989).

Although BECTS is defined as a benign syndrome, implying in the strictest sense its occurrence in otherwise healthy children with normal neuroimaging, there are several reports of BECTS occurring in children with non-rolandic CNS pathology (Beaussart, 1972; Kramer *et al.* 2002, Lundberg *et al.* 1999, Stephani and Dose, 1999, Santanelli *et al.* 1989, Shevell *et al.* 1996). In a series of 71 BECTS cases (Gelisse *et al.* 2003), 14% were found to have rather non-specific abnormalities on neuroimaging, the most common one being enlargement of the ventricles. However, all cases had typical EEG features of BECTS and final recovery occurred in all cases that reached puberty.

Several authors consider that neuroimaging is unnecessary in typical cases of BECTS. In the presence of atypical electroclinical features or abnormalities on neurological examination, an MRI is advocated (Shevell *et al.* 1996, Wirrell, 1998, Holmes, 1993, Gelisse *et al.* 2003). Because the course of BECTS in children with lesions found on neuroimaging is as favorable as in children with no CNS pathology (Lerman and Kivity, 1975), and considering the relatively high incidence of BECTS, many agree that the occurrence of BECTS in a child with CNS pathology is coincidental. However, others suggest that a brain lesion may lower the epileptogenic threshold in children with centrottemporal spikes (Santanelli *et al.* 1989, Gelisse *et al.* 2003). Shevell *et al.* (1996) have proposed that focal lesions, occurring during a particular time of brain development, and brain malformations, mimic the electroclinical features of BECTS, and called this syndrome pseudo-BECTS.

Differential diagnosis

Differentiating BECTS seizures from other partial seizures based on EEG findings is straightforward. Clinically, BECTS is differentiated from complex partial temporal lobe seizures by the absence of aura, automatisms, and psychic phenomena in BECTS (Manelis and Dublin, 1995). Several clinical features distinguish BECTS from BCEOP (see below).

While CSWSS can occur in or can evolve in both Landau-Kleffner syndrome (LKS) and BECTS, BECTS may still be differentiated from LKS by the absence of a distinct, progressive, and prolonged language deficit in the former. The distinction between partial status epilepticus of BECTS and atypical benign idiopathic focal epilepsy lies in the fact that atonic seizures are the most prominent feature of the latter (Gregory *et al.* 2002, Arzimanoglou *et al.* 2004).

Genetics of BECTS

The prevalence of BECTS and other seizure types is increased in the relatives of patients with BECTS (Wirrell, 1998). The EEG finding of centrotemporal spikes suggests an autosomal dominant mode of inheritance (Bray and Wiser, 1964). However, the clinical syndrome of BECTS is considered to have a complex and multi-factorial mode of inheritance (Vadlamudi *et al.* 2006, Wirrell, 1998). A linkage analysis study has shown a susceptibility locus in a region of chromosome 15q14, with peak scores found in a region coding for the alpha 7 subunit of the acetylcholine receptor (Neubauer *et al.* 1998).

Two other BECTS-associated genetic syndromes have been reported. Autosomal dominant rolandic epilepsy with sleep dyspraxia—a syndrome combining features of BECTS, LKS, and epilepsy with CSWSS—is autosomal dominant with 100% penetrance for speech dyspraxia, and exhibits clinical anticipation (Scheffer *et al.* 1995). In a family in which three members were affected by rolandic epilepsy, paroxysmal exercise-induced dystonia, and writer's cramp, linkage analysis revealed a common homozygous haplotype within the region on chromosome 16p12-q12 linked to infantile convulsions and choreoathetosis (ICCA) (Guerrini *et al.* 1999, Szepietowski *et al.* 1997).

Management and prognosis of BECTS

Because isolated, single seizures occur in up to 13% of cases, it is generally agreed upon that AED therapy should be withheld following the first seizure (Wirrell, 1998, Lerman and Kivity, 1975, Ambrosetto and Tassinari, 1990). Proposed indications for AED therapy include a second seizure, seizure-onset prior to the age of four, recurrent generalized tonic-clonic seizures, and diurnal seizures (Wirrell, 1998, Al-Twaijri and Shevell, 2002, Bouma *et al.* 1997, Loiseau *et al.* 1998). AED therapy may not affect seizure frequency, number of seizures, or duration of active epilepsy (Ambrosetto and Tassinari, 1990). Carbamazepine is the most commonly used, initial AED. It is successful in controlling seizures in 50-65% of patients (Wirrell, 1998). Other AEDs used with success include clonazepam (Mitsudome *et al.* 1997), levetiracetam (Bello-Espinosa and Roberts, 2003), gabapentin (Bourgeois *et al.* 1998), phenytoin, valproate, clobazam, primidone, and phenobarbital (Bouma *et al.* 1997; Prats *et al.* 1997). Sulthiame, in a randomized controlled trial, produced initial response rates of 96% (Rating and Wolf, 2000, Dooze *et al.* 1988).

The rare aggravation of BECTS by AEDs has most commonly been reported with carbamazepine, phenobarbital, and less frequently with valproate (Papazian *et al.* 1995, Corda *et al.* 2001). The exacerbation is often associated with the development of CSWSS (Prats *et al.* 1997). Prats *et al.* (1997) reported six patients treated with carbamazepine or valproate who exhibited worsening of clinical seizure and neuropsychological deterioration, with evolu-

tion to LKS in four and ABFCE with or without an operculum-like syndrome in two. Discontinuation of the drug and initiation of alternative therapy resolved the exacerbation in all reported cases.

Failure of AED therapy to control seizures within one year from initiation varies from 14-30%, although this may not correlate with final outcome (Wirrell, 1998). The presence of atypical clinical features may not necessarily influence response to AEDs (Wirrell *et al.* 1995). Length of therapy is controversial; one year may be sufficient (Braathen *et al.* 1996). The relapse rate following AED discontinuation is approximately 14% (Bouma *et al.* 1997).

The natural course of BECTS is one of resolution by mid-adolescence. The mean duration of active seizures is less than three years (Bouma *et al.* 1997). Age-at-seizure cessation ranges from a mean age of 9.6 years (Loiseau *et al.* 1998) to 10.4 years (Kramer *et al.* 2002). Earlier remission occurs in those with seizure-onset after the age of four (Wirrell, 1998) and those with sporadic seizures or seizures that occur in clusters. Between 98% (Loiseau *et al.* 1998) to 99.8% (Bouma *et al.* 1997) remain in remission beyond 18 years of age. However, the relative risk of subsequent GTCS in BECTS patients was found to be ten times greater than that of the general population (Loiseau *et al.* 1998).

While neuropsychological deficits are common during the active phase of the disease, they typically remit following remission of seizures and EEG abnormalities, although mild deficits in executive function may persist (Baglietto *et al.* 2001, Lindgren *et al.* 2004, Loiseau *et al.* 1998, Deonna *et al.* 2000, Loiseau *et al.* 1983). BECTS patients followed-up into adulthood have average or above average social and occupational adjustment (Loiseau *et al.* 1983, Loiseau *et al.* 1998).

Dooze and Baier, (1989) have proposed that "BECTS is only one part of a spectrum caused by a 'hereditary impairment of brain maturation' ", and suggested that patients along the spectrum have specific, inherited EEG features; their place on the spectrum depends on several factors, including localization, the extent of brain maturation or its disturbance thereof, and other genetic and environmental factors. Other disorders in this spectrum include: *benign partial epilepsy with extreme somatosensory evoked potentials; benign childhood epilepsy with affective symptoms; benign childhood epilepsy with occipital paroxysms; atypical benign focal childhood epilepsy; epilepsy with continuous spike-waves during slow sleep and Landau-Kleffner syndrome.*

Atypical evolutions of BECTS

Certain patients with status epilepticus of BECTS, atypical evolutions of BECTS, and atypical evolutions of BCEOP (Caraballo *et al.* 2001, Tenenbaum *et al.* 1997, Fejerman *et al.* 1991) develop CSWSS and clinical features that overlap with LKS, ECSWSS or ABFCE. Together, these patients show several electroclinical features typical of the

epileptic encephalopathies in which CSWSS occur (figure 2).

Fejerman *et al.* (2000) described, among 378 BECTS cases, 26 children with normal initial psychomotor development, normal neuroimaging, and no abnormalities on neurological examination but who later exhibited the atypical evolutions of BECTS. Thus, less than 1% of children with BECTS will evolve to have more complicated disorders. Based on EEG or early seizure characteristics, it is not possible to predict an atypical evolution (Fejerman *et al.* 2000, Nicolai *et al.* 2006).

Atypical partial benign epilepsy (ABFCE), described by Aicardi and Chevrie (1982) and also termed “pseudo-Lennox syndrome” (Hahn, 2000) is characterized by rare, focal and often nocturnal seizures, and by periods, usually of a few weeks in duration, in which intense clinical and

EEG epileptic activity is evident. During these periods, the seizures are characteristically atonic attacks that can be focal or generalized and that can result in multiple daily falls. The EEG abnormalities include brief discharges of spike-waves associated with the falls and CSWSS. The cognitive and behavioral outcome may be favorable, but deterioration may also occur, especially when multiple and long bouts of seizures occur. This condition probably represents an intermittent form of the syndrome of CSWSS (Arzimanoglou *et al.* 2004). In addition to idiopathic ABFCE, a symptomatic variant in which patients exhibit similar electroclinical features but who are found to have gross brain abnormalities on neuroimaging, has also been reported (Aicardi, 2000). Similarly, a minority of patients with BECTS will, years later, develop LKS with CSWSS on EEG (Fejerman *et al.* 2000, Aicardi, 2000).

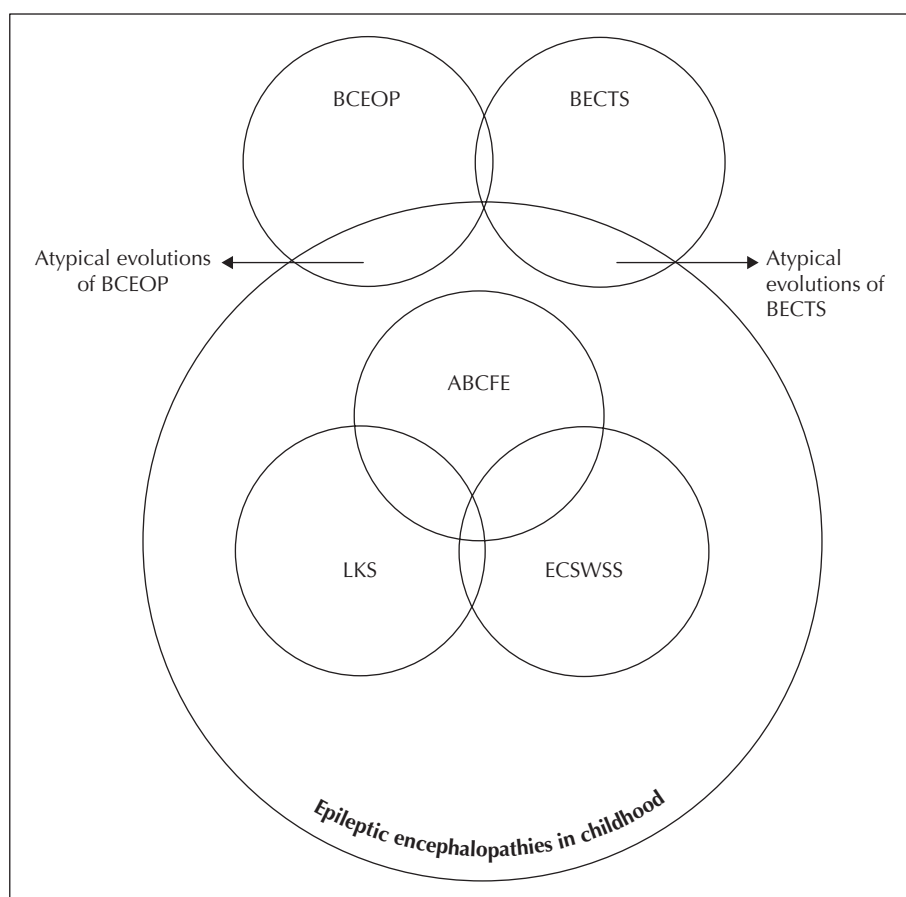


Figure 2. The epileptic encephalopathies of childhood include ABFCE, LKS, and ECSWSS. In addition, atypical evolutions of BCEOP, partial status epilepticus of BECTS, and atypical evolutions of BECTS share several overlapping electroclinical features with each other and with the other epileptic encephalopathies of childhood with the EEG finding of CSWSS.

BCEOP = benign childhood epilepsy with occipital paroxysms. BECTS = benign epilepsy with centrotemporal spikes. ECSWSS = epilepsy with continuous spike-waves during slow-wave sleep. ABFCE = atypical benign focal childhood epilepsy (pseudo-Lennox Gastaut). LKS = Landau-Kleffner syndrome.

Benign childhood epilepsy with occipital paroxysms (BCEOP)

Benign childhood epilepsy with occipital paroxysms (BCEOP), initially described by Gastaut (1982), has been classified under the idiopathic, localization-related epilepsies (Commission on Classification and Terminology of the International League Against epilepsy, 1989). However, with the recognition of a distinct entity with an earlier age-at-onset described by Panayiotopoulos in 1989, it was proposed to recognize two different syndromes: early-onset benign occipital seizure susceptibility syndrome (**Panayiotopoulos syndrome**) and late-onset childhood occipital epilepsy (**Gastaut type BCEOP**) (Engel, 2001). They will be referred to as Gastaut-type BCEOP and Panayiotopoulos-type BCEOP. Similarities and differences between the two conditions are summarized in *table 2*.

Epidemiology

In one series, Gastaut-type BCEOP constituted 0.15% of all localization-related epilepsies (Oguni *et al.* 1999). The prevalence of Panayiotopoulos-type BCEOP is reported to range from 6.7% (Lada *et al.* 2003) to 13% among children with localization-related epilepsies (Oguni *et al.* 1999, 2001).

Clinical manifestations of Panayiotopoulos-type BCEOP

Onset is reported between the ages of two and twelve years, with a mean age of five years. Large cohorts have not demonstrated gender predominance (Panayiotopoulos, 1999b). There is a history of febrile seizures in 4.4% (Lada *et al.* 2003) to 25% (Caraballo *et al.* 2000), and a history of migraine in 15% (Oguni *et al.* 1999). Seizures are nocturnal in 80% (Lada *et al.* 2003, Caraballo *et al.* 2000). Seizure onset is usually marked by ictal vomiting, although only nausea or retching may occur. While vomiting has been cited to occur as the initial event in 60-80% (Lada *et al.* 2003, Koutroumanidis, 2002, Panayiotopoulos, 2001, Oguni *et al.* 1999), others have reported a frequency of only 44% (Kivity *et al.* 2000). Vomiting is accompanied or followed by tonic eye, and less commonly head, deviation in 70-98% (Oguni *et al.* 1999, Caraballo *et al.* 2000). Alternatively, tonic eye deviation was reported to occur without vomiting. In one series of 134 patients, 100% had tonic eye deviation whereas only 44% had ictal vomiting (Kivity *et al.* 2000). Autonomic manifestations, including urine incontinence, pallor, perioral cyanosis, hypersalivation, and rarely, ictal headache and fecal incontinence may occur (Lada *et al.* 2003, Ferrie and Grunewald, 2001, Koutroumanidis, 2002). Impairment of consciousness is invariable (Lada *et al.* 2003). Rarely, BECTS-like features such as speech arrest, hemifacial spasm, and oropharyngeal involvement also occur (Covanis *et al.* 2003, Koutroumanidis 2002, Caraballo *et al.* 1998). Visual hallucinations are rare,

occurring in less than 10% (Panayiotopoulos 2001, Caraballo *et al.* 2000).

In 30-50% of patients, progression to hemiconvulsions or generalized tonic-clonic seizures (GTCS) occurs (Lada *et al.* 2003, Panayiotopoulos 2001, Koutroumanidis 2002, Oguni *et al.* 1999). Partial or complex partial status epilepticus, marked by tonic eye or head deviation, with or without concomitant vomiting occurs in 30%-50% of cases. The occurrence of status epilepticus is more common in those with ictal vomiting (Koutroumanidis 2002, Oguni *et al.* 1999, Kivity and Lerman 1992). Partial status epilepticus evolves into hemiconvulsions in up to 34% and secondarily generalizes in 16%-25% (Ferrie *et al.* 1997, Caraballo *et al.* 2000).

In 33% of cases, seizures last 2 to 10 minutes (Kivity *et al.* 2000, Kivity and Lerman 1992). Seizure frequency is highly variable, ranging from an isolated seizure in 18-53% to more than several seizures per month in 5-26% (Koutroumanidis 2002, Caraballo *et al.* 2000, Oguni *et al.* 1999, Lada *et al.* 2003, Ferrie *et al.* 1997). Status epilepticus may occur recurrently, particularly in children with younger age-at-seizure onset and in those with ictal vomiting (Oguni *et al.* 2001, Kivity *et al.* 2000). Patients with even the most florid, prolonged seizures will return to baseline after a few hours (Koutroumanidis 2002, Ferrie and Grunewald 2001).

Clinical manifestations of Gastaut-type BCEOP

The Gastaut-type BCEOP begins later in life, between the ages of 3-16 years, with a mean age of 7.4-8 years. There is no sex predominance (Panayiotopoulos 1999b). Seizures are diurnal in over 80% (Kivity *et al.* 2000). Seizure onset is marked by visual phenomena, most commonly amaurosis (Gastaut 1982), or elementary or complex visual hallucinations (Panayiotopoulos 1999a). In 44% of Gastaut's original series (1982), visual hallucinations were followed by hemiclonic seizures or automatisms, with or without secondarily generalization. Adversive manifestations may accompany the visual phenomena or occur alone in a minority. Ictal vomiting and headache rarely occur; postictal, migrainous headache, with or without nausea and/or vomiting occurs in 25% (Panayiotopoulos 1999a).

Seizure duration is typically less than 5 minutes (Tsai *et al.* 2001); visual hallucinations last one to 3 minutes and ictal blindness usually lasts 3 to 5 minutes (Panayiotopoulos 1999a). Status epilepticus marked by behavioral and cognitive disturbances may rarely occur (Panayiotopoulos 1999a, Caraballo *et al.* 2000). During the visual hallucinations, consciousness is preserved but may be altered should the seizure progress. Isolated seizures rarely occur; more than two-thirds of patients will have at least four seizures; many will have daily to monthly seizures (Panayiotopoulos 1999b, Kivity *et al.* 2000, Tsai *et al.* 2001).

Table 2. Comparison of Gastaut-type BCEOP and Panayiotopoulos-type BCEOP.

	Gastaut-type BCEOP	Panayiotopoulos -type BCEOP
Epidemiology	Constitutes 0.15% of cases of childhood localization-related epilepsies	Constitutes 13% of cases of childhood localization-related epilepsies
Age-at-onset	3-16 with a mean age of 7.4-8 years	2-12 with a mean age of 5 years
Most prominent clinical manifestations	Diurnal in over 80% Visual phenomena at seizure-onset, usually accompanied by adverse manifestations, followed in some by hemiclonic seizures or automatisms, with or without secondary generalization. Postictal migrainous headache, with or without nausea and/or vomiting Status epilepticus rare	Nocturnal in 80% Ictal vomiting and/or tonic eye deviation at seizure onset Autonomic manifestations in some Progression to hemiconvulsions or GTCS in 50% of patients Status epilepticus common
Visual hallucinations	Often present	Rare
Ictal vomiting	Rare	Often present
Impairment of consciousness	Rare unless seizure progresses	As a rule initially not present (simple partial) then occurs in almost all (complex partial)
Seizure frequency	Isolated seizures rarely occur Majority have at least four seizures; many have daily to monthly seizures	Highly variable One third to half have isolated seizures
Seizure duration	Seizure duration typically less than 5 minutes Visual hallucinations last 1-3 minutes Ictal blindness lasts 3-5 minutes	Seizure duration 2-10 minutes in one-third of patients Autonomic status, lasting longer than 30 minutes, in one third to half
Interictal EEG	Occipital spikes usually showing fixation off sensitivity (block with eyes open while fixing)	Spikes most commonly occipital but often multi-focal, frequently parietal
Ictal EEG findings	Cessation of sharp-wave occipital discharges followed by 10 Hz spike discharges or other fast rhythms in the occipital region and then slow monomorphic activity or spike-waves localized to the posterior areas	Rhythmic monomorphic decelerating theta or delta activity Often initially occipital and lateralized at onset with later spread to other regions, though ictal onset in other areas has been described
Dipole of occipital spikes	Superficial	Deep
Diagnostic criteria	Normal psychomotor development Normal neuroimaging Age of seizure onset between 3-16 Seizures marked by ictal blindness and/or visual hallucinations that may be followed by hemiclonic convulsions Occipital EEG foci with or without foci migration or foci in other locations Remission by late teenage-hood	Normal psychomotor development Normal neuroimaging Age of seizure onset between 2-12 years Infrequent partial seizures marked by vomiting and tonic eye and/or head deviation with or without hemiconvulsions or secondary generalization Occipital EEG foci with or without foci migration or foci in other locations Seizure remission by age 12
Prognosis	In 60%, remission occurs in the late teens In 30-40% of cases, visual seizures with or without secondary GTCS continue to occur and become difficult to control	In 50-60%, remission occurs within 1-2 years of seizure onset Majority of patients remit by age 12

Neuropsychological features of BEOCP

To our knowledge, the neuropsychological features of Gastaut-type BCEOP have not been studied. During the active phase of their disease, Panayiotopoulos type BCEOP patients show lower IQ scores compared to

controls (Oguni *et al.* 2001), and verbal tasks are particularly impaired. They have an increased frequency of selective learning disabilities, and perform significantly lower on tasks of manual dexterity, global visual perception, visual-motor integration, and visual attention compared to controls (Germano *et al.* 2005).

EEG findings in BCEOP

Panayiotopoulos-type BCEOP and Gastaut-type BCEOP share similar interictal EEG features (Ferrie *et al.* 1997, Gastaut, 1982, Verrotti *et al.* 2000, Tsai *et al.* 2001), although differences, particularly in sleep EEG recordings, have been reported (Panayiotopoulos 1989, Fejerman 1997, Caraballo *et al.* 1994). Background activity is normal. In the majority of patients, interictal EEG is marked by high amplitude (200–300 μ V) spikes followed by slow-wave discharges recurring rhythmically at 2–3 second intervals, classically described as being in the occipital region, although it is increasingly being recognized that this is not systematically the case in Panayiotopoulos-type BCEOP (Ferrie *et al.* 1997, Panayiotopoulos, 1999a, Gastaut, 1982). Most occipital paroxysms occur during eye closure and are suppressed by eye-opening (Tsai *et al.* 2001, Panayiotopoulos, 1999a). They may be bilateral or unilateral, in which case they are more often right-sided (Lada *et al.* 2003, Tsai *et al.* 2001). These spike-waves may be synchronous or asynchronous, and symmetric or asymmetric.

That the dipole of occipital spikes is superficially located in Gastaut-type BCEOP (Van der Melj *et al.* 1997) but not in Panayiotopoulos-type BCEOP (Yoshinaga *et al.* 2005) may account for the absence of visual symptoms in most Panayiotopoulos syndrome cases.

Fixation-off sensitivity (FOS), the occurrence of interictal discharges as the result of elimination of central vision and fixation, is a feature of both types of BCEOP (Panayiotopoulos, 1989, Panayiotopoulos, 1998a). Fixation-off sensitivity occurs less commonly in other conditions as compared to BCEOP (Kivity *et al.* 2000, Panayiotopoulos, 1998a). Intermittent photic stimulation and sleep do not increase the occurrence of spike-waves in Gastaut-type BCEOP, but this has been rarely reported to occur in Panayiotopoulos-type BCEOP (Gastaut, 1982, Lada *et al.* 2003).

EEG findings in Panayiotopoulos-type BCEOP

Interictal EEG is initially normal in up to 25% of cases (Kivity *et al.* 2000); discharges will be seen in subsequent EEGs in the majority (Panayiotopoulos, 1999b, Guerrini *et al.* 1997). While spikes are classically occipital, many patients have spikes in other regions, either alone or in combination, in parietal, centrotemporal, frontal, multifocal, or brief bursts of generalized spike-waves (Lada *et al.* 2003, Koutroumanidis, 2002, Caraballo *et al.* 2000, Kanazawa *et al.* 2005). Combinations of occipital spikes with any of the latter may also occur. In fact, the frequently parietal origin of discharges has led some to question the accuracy of classifying the Panayiotopoulos-type BCEOP as occipital epilepsy (Kanazawa *et al.* 2005). Recently, it has been suggested to classify this syndrome as an autonomous form of epilepsy (Ferrie *et al.* 2006). Clinical manifestations do not vary according to spike location or fre-

quency (Lada *et al.* 2003). In some cases, occipital spikes on EEG will only be present postictally (Kivity *et al.* 2000). Occipital spike-waves on EEG shift in location to more anterior sites with increasing age (Oguni *et al.* 1999, Oguni 2001, Ohtsu *et al.* 2003).

Vigevano *et al.* (2000) reported on an ictal EEG of a Panayiotopoulos-type BCEOP. The tracing showed rhythmic or arrhythmic, high amplitude slow waves of 2 Hz frequency, with intermixed spikes or polyspikes with right occipital localization that later spread to right temporal and contralateral occipital regions. This activity did not vary throughout the seizure. The seizure ended abruptly with diffuse, low voltage activity, followed by postictal delta rhythm activity of high voltage in the right occipital region that lasted for several minutes. Others have also reported ictal shifting of initially unilateral occipital spikes to bilateral occipital regions. In another description of an ictal EEG, cessation of occipital paroxysms and the occurrence of sharp rhythms in the occipital region, progressing to monomorphic theta activity bilaterally, were described (Panayiotopoulos, 1999a). Others have reported origination of seizure discharges in extra-occipital areas, such as the unilateral frontal region in one report (Oguni *et al.* 2001).

MEG studies on Panayiotopoulos-type BCEOP patients localized clustered equivalent current dipoles to areas near the parieto-occipital sulcus, calcarine sulcus, or both in eight patients and to the centrotemporal area in two (Kanazawa *et al.* 2005).

EEG findings in Gastaut-type BCEOP

Beaumanoir (1983) reported EEG manifestations of a diurnal seizure in a patient with Gastaut-type BCEOP (figure 3). Ictal EEG showed focal rapid spike-waves that progressively slowed. A nocturnal ictal EEG recording showed cessation of sharp-wave occipital discharges followed by 10 Hz spike discharges in the occipital region and then slow, monomorphic activity or spike-waves localized to the posterior areas. Thomas *et al.* (2003) published a case with a video-recording of several ictal events.

Work-up and diagnostic criteria

The presence of typical electroclinical features is diagnostic of both types of BCEOP although EEG abnormalities are not a prerequisite for the diagnosis of Panayiotopoulos-type BCEOP (Ferrie *et al.* 1997, Gastaut, 1982, Panayiotopoulos, 1989). A sleep EEG should be performed if the EEG is normal in a patient with suspected Panayiotopoulos syndrome (Koutroumanidis, 2002).

Diagnostic criteria of Panayiotopoulos-type BCEOP

The diagnostic criteria of Panayiotopoulos-type BCEOP include: i) normal psychomotor development; ii) normal neuroimaging; iii) age-at-seizure onset between 2–12 years; iv) infrequent partial seizures marked by vomiting and tonic eye and/or head deviation with or without

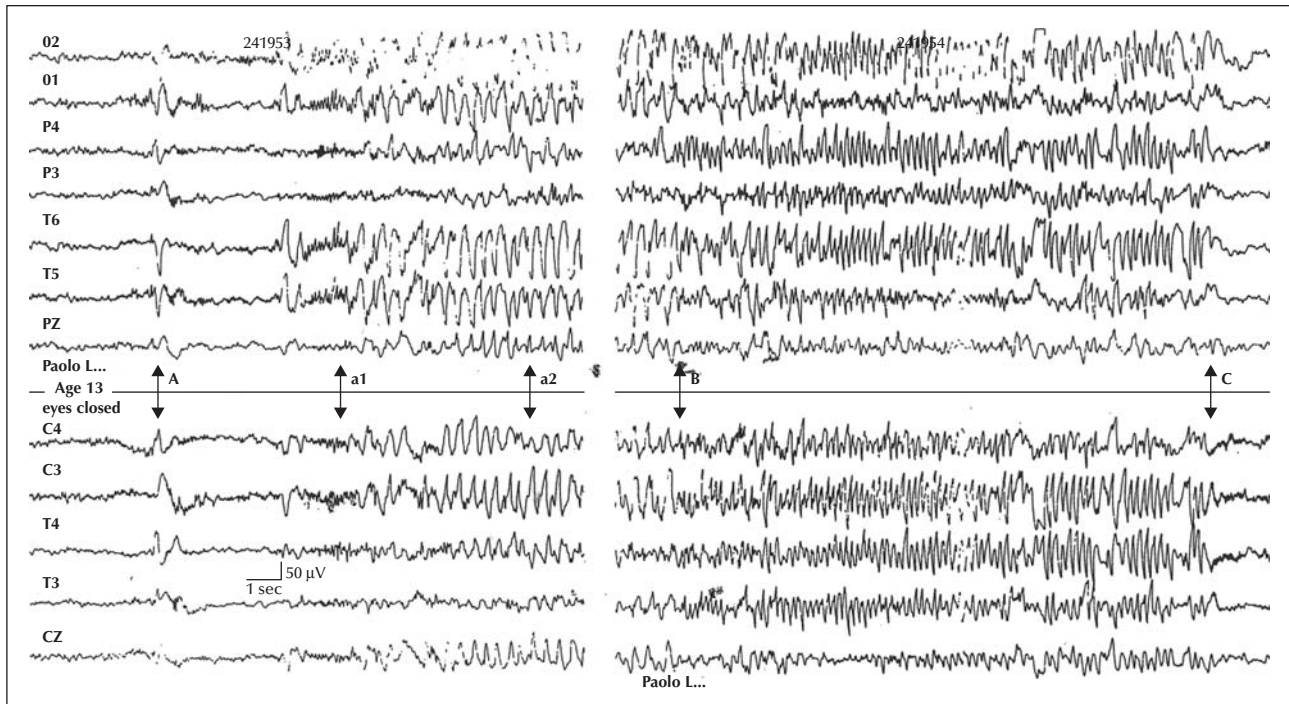


Figure 3. Ictal EEG in a patient with Gastaut-type BCEOP showing occipital and posterior temporal ictal discharges with a right-hemispheric predominance (reproduced with kind permission of John & Libbey Eurotext from Roger J, Dravet C, Bureau M, Dreifuss FE, Perret A, Wolf P, eds. *Epileptic syndromes in infancy, childhood, and adolescence* (2nd edition). London: John Libbey Eurotext, 1992). At **A**, the child said “Here it comes! I see yellow”. At a1 and a2, he was asked what he saw and described “the lights of a car at night”. At **B**, he turned his head and eyes to the left and did not respond. At **C**, he suddenly asked “where am I?”.

hemiconvulsions or secondary generalization; v) occipital EEG foci with or without foci migration or foci in other locations; and vi) seizure remission by age 12 (Oguni *et al.* 1999).

Diagnostic criteria of Gastaut-type BCEOP

The diagnostic criteria of Gastaut-type BCEOP are less well-defined. They should probably include: i) normal psychomotor development; ii) normal neuroimaging; iii) age-at-seizure onset between 3-16; iv) seizures marked by ictal blindness and/or visual hallucinations that may be followed by hemiclonic convulsions; v) occipital EEG foci with or without foci migration or foci in other locations; and vi) remission by late teenagehood.

Differential diagnosis of Panayiotopoulos-type BCEOP

The ictus emeticus typical of Panayiotopoulos-type BCEOP rarely occurs in other childhood epilepsies (Panayiotopoulos, 1988).

Some patients with Panayiotopoulos syndrome may exhibit features of BECTS; in all these cases other distinguishing features will be present; ictus emeticus, a prominent feature of the syndrome, is very rarely present in BECTS (Covanis *et al.* 2003). In doubtful cases, an MRI can help differentiate Panayiotopoulos-type BCEOP from mesial

temporal lobe epilepsy with hippocampal sclerosis (Oguni *et al.* 1999).

The inaugural event of Panayiotopoulos-type BCEOP may be prolonged seizures; this may mistakenly be attributed to a cerebral insult, and extensive concern and undue work-up may ensue. The most reliable feature differentiating Panayiotopoulos-type BCEOP from more serious disorders are EEG findings and the return to baseline of the child within a few hours of sleep in the former (Caraballo *et al.* 2000, Kivity and Lerman, 1992).

Panayiotopoulos-type BCEOP may be differentiated from idiopathic photosensitive occipital epilepsy in which ictus emeticus may occur, in that the latter is triggered by photic stimulation and often accompanied by visual hallucinations, blurry vision, or amaurosis (Guerrini *et al.* 1995, Caraballo *et al.* 2000).

Differential diagnosis of Gastaut-type BCEOP

Earlier age-at-onset, the presence of ictal vomiting, a nocturnal predominance for seizures, and absence of visual hallucinations that characterize the Panayiotopoulos type are helpful, differential diagnosis clues (*table 2*).

A careful history will differentiate Gastaut-type BCEOP from idiopathic photosensitive occipital epilepsy, as sei-

zures in the former are spontaneous rather than visually induced (Guerrini *et al.* 1995).

It was initially suggested that the seizures of what is now known to be BCEOP were manifestations of basilar migraine (Panayiotopoulos, 1980). A detailed history makes the differentiation between occipital seizures and migraine possible (Panayiotopoulos, 1999d).

Several features of seizures in Gastaut-type BCEOP patients occur in patients with symptomatic occipital lobe epilepsy, including visual hallucinations and tonic eye deviation. The EEG may be useful in distinguishing between them, but not in all cases. Contrary to what is suggested in patients with BECTS, an MRI is often necessary in patients with a suspicion of Gastaut-type BCEOP in order to eliminate the presence of a lesion indicative of a symptomatic occipital epilepsy. Dipole source analysis may also distinguish the two syndromes (Van der Meij *et al.* 1997).

Genetics of BCEOP

No single gene has been linked to BCEOP. The occurrence of Gastaut-type BCEOP in several family members has been reported (Kellerman, 1993, Nagendra and Rossiter, 1990). In Gastaut's (1982) original description of BCEOP, a family history of epilepsy was present in 47% and of migraine in 19%.

A history of seizures is present in between 7% (Lada *et al.* 2003) to 32% (Caraballo *et al.* 2000, Oguni *et al.* 2001) of family members of patients with Panayiotopoulos-type BCEOP. Thus, a genetic background predisposing to both types of BCEOP appears likely.

Management and prognosis

Since up to half of Panayiotopoulos-type BCEOP patients experience only one seizure, it is generally agreed upon that initiation of AED therapy is not indicated following the first seizure, but should be considered after the second seizure or following status epilepticus (Lada *et al.* 2003, Oguni *et al.* 1999). A higher seizure frequency is more common in Gastaut-type BCEOP and earlier treatment may be indicated (Tsai *et al.* 2001). For both types of BCEOP, carbamazepine has been the most commonly used AED, although oxcarbazepine, valproic acid, clobazam, and even phenobarbital have also been used (Ferrie *et al.* 1997, Gastaut, 1982, Verrotti *et al.* 2000). Withdrawal of treatment within one to two years is generally advised regardless of persistence of EEG abnormalities (Ferrie and Grunewald, 2001, Oguni *et al.* 1999). As in BECTS, exacerbation of Panayiotopoulos-type BCEOP by carbamazepine therapy has been reported (Kikumoto *et al.* 2006).

In 50-60% of Panayiotopoulos-type BCEOP patients, remission occurs within one to two years of seizure-onset (Panayiotopoulos, 1999a). The majority of Panayiotopoulos-type BCEOP patients remit by age 12

(Oguni *et al.* 1999). Although it has been reported that 85-90% of Panayiotopoulos-type BCEOP patients remit on carbamazepine (Panayiotopoulos, 1999a, Ferrie *et al.* 1997), other studies have shown failure of remission on carbamazepine monotherapy in 15-30% (Ferrie *et al.* 1997, Oguni *et al.* 2001). The occurrence of partial status epilepticus does not influence final prognosis (Koutroumanidis, 2002). Some patients, particularly those with frequent seizures and recurrent status epilepticus, may require trials of different AEDs and occasionally more than one AED for seizure control (Oguni *et al.* 2001). BECTS will occur in approximately 5% of Panayiotopoulos-type BCEOP patients within two to three years of remission and will remit by the age of 16 (Koutroumanidis, 2002, Oguni *et al.* 1999, Berg and Panayiotopoulos, 2000, Caraballo *et al.* 1998). Atypical evolutions of BCEOP have been reported but are rather uncommon (Caraballo *et al.* 2001, Ferrie *et al.* 2002, Caraballo *et al.* 2005, Tenembaum *et al.* 1997, Fejerman *et al.* 1991).

Although one study found no statistically significant difference between the two forms of BCEOP (Tsai *et al.* 2001), Gastaut-type BCEOP patients are generally cited as having a less certain prognosis. In 60% of these patients, remission is reported to occur in the late teens although persistence of seizures into late teenagehood may occur (Panayiotopoulos, 1999a, Panayiotopoulos, 1999b). Gastaut (1982) reported, in his original series, that 92% of patients reached full clinical remission by age 19; 53% remitted with initiation of AED therapy. Response rates of up to 90% have been reported (Panayiotopoulos, 1999a, Tsai *et al.* 2001). In 30-40% of cases, visual seizures with or without secondary generalization continue to occur and become difficult to control (Panayiotopoulos, 1999a, Panayiotopoulos, 1999b).

Intellectual outcome following seizure remission is generally normal, although 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).

Special considerations in the treatment of the benign localization-related epilepsy syndromes: interictal EEG abnormalities

Persistence of interictal EEG abnormalities despite remission of clinical seizures is a feature of several benign epilepsy syndromes including BECTS (Wirrell, 1998), BCEOP (Panayiotopoulos, 1989, Caraballo *et al.* 2000), and the newly defined benign infantile focal epilepsy with midline spikes and waves during sleep [previously known as benign partial epilepsy in infancy and early childhood with vertex spikes and waves (Capovilla and Beccaria, 2000, Capovilla *et al.* 2006, Chahine and Mikati, 2006)]. The significance of interictal abnormalities in these patients is unclear, yet they may account for some neuropathology.

psychological deficits found (Saint-Martin *et al.* 2001b). Most investigations on this issue have focused on BECTS. BECTS patients exhibit cognitive and behavioral problems during the active phase of their disease (Massa *et al.* 2001, Weglage *et al.* 1997, Nicolai *et al.* 2006). A mild epileptic encephalopathy may account for these abnormalities (Sanchez-Carpintero and Neville, 2003); nocturnal interictal abnormalities are particularly implicated (Baglietto *et al.* 2001). In the majority, neuropsychological follow-up, following clinical seizure remission, normalizes with the exception of mild deficits in executive function, particularly in tasks of verbal ability (Lindgren *et al.* 2004). While sleep organization in BECTS patients is normal (Dalla-Bernardina and Beghini, 1976), approximately 30% of children with BECTS have EEG abnormalities only during sleep (Nicolai *et al.* 2006), and sleep increases interictal abnormalities (Baglietto *et al.* 2001). Non-REM sleep has been shown to activate them (Shouse *et al.* 2004). Sigma activity may play a more important role than slow-wave activity in activating interictal abnormalities in BECTS patients (Nobil *et al.* 1999). Interictal EEG abnormalities remit spontaneously in the majority; "treatment" of these abnormalities, in the absence of clinical seizures is controversial, but may be of benefit in some cases (Deonna *et al.* 2000, Baglietto *et al.* 2001). Sulthiame, diazepam, and clonazepam are reported to decrease EEG discharges in BECTS (Bast *et al.* 2003, Mitsudome *et al.* 1997, De Negri *et al.* 1997). Small studies have found that treatment of nocturnal interictal discharges with diazepam improves cognitive and behavioral problems in BECTS (De Negri *et al.* 1997, Baglietto *et al.* 2001). Currently, there are no large, controlled studies that have demonstrated which patients may benefit from such treatment. Treatment in the absence of clinical seizures may also be indicated in some children with cognitive problems that impact daily life (Deonna *et al.* 2000, Baglietto *et al.* 2001), but controlled studies are not available.

Conclusion

Over recent decades it has been increasingly recognized that certain patients with epilepsy have no underlying neurological abnormalities, have seizures that respond well to AED therapy, and remit without sequelae. Recent years have seen an increase in studies describing the childhood-localization related epilepsy syndrome BECTS and BCEOP. Though some patients diagnosed with BECTS or BCEOP exhibit atypical evolutions and/or show persistent neuropsychological deficits, the majority of patients with these childhood localization-related epilepsy syndromes follow a truly benign course. Prognosticating at seizure-onset which patients will follow a truly benign course is not possible at this time, hence the utility of using possible, probable, and definite designations while classi-

fying epilepsy syndromes (Chahine and Mikati, 2006). More studies are needed to derive such prognostic information. Studies investigating the significance of interictal EEG abnormalities and how they are best managed are also needed. □

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