Benign occipital epilepsies of childhood: clinical features and genetics

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The early and late benign occipital epilepsies of childhood (BOEC) are described as two discrete electro-clinical syndromes, eponymously known as Panayiotopoulos and Gastaut syndromes. Our aim was to explore the clinical features, classification and clinical genetics of these syndromes using twin and multiplex family studies to determine whether they are indeed distinct. Sixteen probands including seven twins were studied. Non-twin probands (n = 9) with a family history of epilepsy were included. Electroclinical seizure semiology was characterized and probands were classified into BOEC syndromes. Detailed phenotyping of relatives was performed and phenotypic patterns within families were analysed. One-third of the children in this selected series of BOEC did not have a pure syndrome, rather a mixed syndrome with features of both Panayiotopoulos and Gastaut syndromes. Monozygotic twin pairs did not show a higher concordance rate than dizygotic twin pairs suggesting that BOEC may not be a purely genetic disorder. In relatives with epilepsy, there was a mixed pattern of focal and generalized epilepsies with focal epilepsies predominating. BOEC is an electro-clinical spectrum with Panayiotopoulos and Gastaut syndromes at either end; many cases show mixed features. Clinical genetic studies highlight the multifactorial aetiology of BOEC as monozygotic twins have low concordance suggesting that non-conventional genetic influences or environmental factors play a major role. Family studies show both focal and generalized epilepsies reinforcing that these are not discrete categories of idiopathic epilepsies and are likely to share genetic determinants.

Keywords: occipital; epilepsy; childhood; genetic; benign

Abbreviations: BOEC = Benign Occipital Epilepsies of Childhood; SCN1A = Sodium Channel, Neuronal type I, Alpha subunit; CT = computed tomography; MRI = magnetic resonance imaging; AED = anti-epileptic drug; EEG = electro-encephalogram; DZ = dizygotic; MZ = monozygotic; GSW = generalized spike and wave; NHMRC = National Health and Medical Research Council; BECTS = benign childhood epilepsy with centrotemporal spikes; JME = juvenile myoclonic epilepsy; CAE = childhood absence epilepsy; MA = myoclonic absence; GTCA = generalized tonic clonic seizures alone; FS+ = febrile seizures plus; TLE = temporal lobe epilepsy; RE = Rolandic epilepsy


Introduction

The benign occipital epilepsies of childhood (BOEC) are classified into two apparently discrete groups comprising an early (Panayiotopoulos) and late (Gastaut) form. Despite an overlapping range of age of onset, each syndrome has been held to have a classical presentation that is quite distinctive and easily differentiated from the other (Caraballo et al., 2007; Koutroumanidis, 2007; Panayiotopoulos, 2007). In Panayiotopoulos syndrome, children present at a mean of 4.7 years (range 1–14 years) with rare seizures which are prolonged and nocturnal. Seizures begin with autonomic features such as vomiting, pallor and sweating followed by tonic eye deviation, impairment of consciousness and may evolve to a hemi-clonic or generalized convulsion. Autonomic status epilepticus may occur. While it was initially regarded as purely an occipital syndrome...
‘early onset benign childhood epilepsy with occipital spikes’), in an important minority of cases there is evidence that regions outside the occipital region generate seizures (Koutroumanidis, 2007). Prognosis is excellent and treatment often unnecessary. Visual hallucinations, ictal blindness and headache are exceptional (Panayiotopoulos, 1989b; Berg and Panayiotopoulos, 2000). Gastaut syndrome, or late onset childhood epilepsy with occipital spikes, presents at a mean of 8 years (range 3–16 years). Seizures are frequent, brief and diurnal. They comprise simple partial seizures characterized by initial visual hallucinations such as phosphenes and/or ictal blindness and illusions (Gastaut, 1982); post-ictal headache is common. Impairment of consciousness is rare unless associated with hemi-clonic or generalized convulsions. Treatment usually involves carbamazepine and seizures remit within 2–5 years (Panayiotopoulos, 1993, 1999, 2000).

Both syndromes share similar classical inter-ictal EEG features with runs of occipital sharp and slow wave complexes which attenuate on eye opening (Panayiotopoulos, 1981). Overlap between clinical features has also been reported (Kivity et al., 2000). We wished to explore these syndromes clinically and from a genetic standpoint to determine whether they are truly separate or whether phenotypic overlap is common. Moreover, the clinical genetics of BOEC have not been well studied so we focused on twins and multiplex families to explore the phenotypes found in families of children with BOEC.

**Methods**

**Subject recruitment**

(1) Twins were identified through a large-scale twin study of the epilepsies, performed at the Epilepsy Research Centre, Austin Health, in collaboration with the Australian NHMRC twin registry (Berkovic et al., 1998b). All twins with BOEC were included.

(2) Non-twin probands were obtained from the First Seizure Clinic of Austin Health, Melbourne, Australia, the Epilepsy Genetics Clinic of the Royal Children’s Hospital, Melbourne, Australia, the Pediatric Epilepsy Unit and EEG Laboratory Schneider Children’s Medical Centre of Israel and from the private clinics of paediatric and adult neurologists and paediatricians.

Non-twin probands were only included if they had a personal history of BOEC and a family history of seizure disorders. ‘Sporadic’ non-twin cases were not recruited.

**Assessment**

Each proband underwent a personal interview using a specially designed questionnaire focusing on the clinical features of each BOEC syndrome. All probands underwent neurological examination and a 21-channel EEG recording. If the initial EEG was normal, probands underwent further sleep deprived EEG study in order to activate ictal epileptiform discharges. An additional midline occipital O2 electrode was utilized in most instances. Neuroimaging was performed where possible and was available in 12 of the 16 cases. Rare patients underwent long-term video-EEG monitoring. Seizure types were then classified.

**Inclusion criteria**

Cases where the electro-clinical diagnosis was consistent with BOEC were included. Cases were however accepted even in the absence of definitive occipital epileptiform discharges as these may be hard to document in a cross-sectional analysis and the EEG may be normal.

**Exclusion criteria**

(i) If subjects were not considered to have an idiopathic epilepsy, that is, if they had abnormal development, abnormal physical examination or laboratory investigations or significant abnormalities on neuroimaging.

(ii) Clinical or EEG photosensitivity, thus excluding the syndrome of idiopathic photosensitive occipital epilepsy (Guerini et al., 1995).

[Probands were not excluded if centrotemporal spikes and/or generalized spike and wave (GSW) were seen on the EEG as long as the seizure semiology was typical of BOEC; as centrotemporal spikes and/or GSW may be seen during the course or following both the Panayiotopoulos (Panayiotopoulos, 1989b; Ferrie et al., 2006; Caraballo et al., 2007) and Gastaut syndromes (Gastaut, 1982).]

**Classification of the Panayiotopoulos and Gastaut syndromes**

The proband was classified as ‘Panayiotopoulos syndrome’ if the proband’s ictal semiology comprised at least five of the following features—onset in early childhood to early adolescence (range 1–14 years), predominantly nocturnal seizures (>2/3 attacks), autonomic features (pallor, sweating), ictal vomiting, impaired consciousness, longer duration (3–30 min or hours) and rare seizures (1–15 in total) (Panayiotopoulos, 2000). If they had additional initial visual hallucinations, ictal blindness and post-ictal headache they were excluded from the Panayiotopoulos syndrome and placed in the ‘mixed’ category.

The proband was classified as ‘Gastaut syndrome’ if the proband’s ictal semiology comprised at least five of the following (Panayiotopoulos, 2000)—onset in childhood to mid adolescence (range 3–15 years), diurnal (>2/3 seizures), brief (seconds to a minute) and frequent seizures (usually >15 in total), prominent initial visual hallucinations, ictal blindness and post-ictal headache. Probands were excluded from this category if their seizure semiology included ictal vomiting and were then placed in the ‘mixed’ category.

Probands were placed in the ‘mixed’ category if their seizure semiology did not convincingly fit into either the Panayiotopoulos or Gastaut syndrome or had features of both.

**Clinical genetic studies**

Family studies were carried out where any family member had a history of seizures. Detailed pedigrees were constructed for each proband with BOEC. Family members with a history of seizures underwent detailed characterization using a validated seizure questionnaire (Reutens et al., 1992). Previous medical records, EEG and imaging results were reviewed. Seizure types and syndromes were classified for each family member where possible. On same-sex twins, zygosity was determined by clinical questionnaire and polymorphic DNA markers.
Results
Distinction of Panayiotopoulos and Gastaut syndromes

The clinical details of 16 patients with BOEC including seven twin probands are summarized in Table 1 (detailed information in Supplementary Table 1).

Six probands had Panayiotopoulos syndrome, five had Gastaut syndrome and five had features of both syndromes. The EEGs showed frank occipital epileptiform activity in nine individuals, posterior quadrant slowing in four, a single left centrotemporal discharge during sleep in one, one was normal and in one proband the records had been destroyed. Of the nine with occipital epileptiform activity, two also had generalized spike and wave (in one only during hyperventilation) and one developed rolandic spikes a year after seizure onset.

Twelve patients had neuroimaging [CT scan (probands 4, 6, 11, 14, 16) or MRI (probands 3, 8, 9, 10, 12, 13, 15)]; 10 scans were normal (probands 3, 4, 6, 8, 10, 11, 13, 14, 15, 16), proband 12 had a thin corpus callosum and proband 9 had a focal linear abnormality of the antero-medial thalamus; these abnormalities were considered incidental. Probands 1, 2, 5 and 7 did not have neuroimaging.

Thirteen probands required treatment with anti-epileptic drugs (AEDs). Of the three who did not, two had Panayiotopoulos syndrome and one had a mixed syndrome. All patients with Panayiotopoulos syndrome had a good prognosis with spontaneous seizure remission or were easily controlled with a single AED. Of the five with Gastaut syndrome, three achieved remission with the first single agent of choice, one achieved remission with the initial AED and then relapsed necessitating a change in therapy and one required dual therapy. Of the five probands with the mixed syndrome, three required dual AEDs to achieve seizure control, one required a single agent and one did not require AED.

Genetics

Twin probands

Seven twin pairs were studied: four dizygotic (DZ) (probands 5, 6, 9 and 14) and three monozygotic (MZ) (probands 4, 11 and 16). One MZ twin pair (proband 4) was concordant for Panayiotopoulos syndrome and one DZ pair (proband 14) was concordant for Gastaut syndrome. Two MZ twins (probands 11 and 16) were discordant with their co-twin unaffected: one had the mixed syndrome and the other Gastaut syndrome. Three DZ twin pairs were discordant: two with Panayiotopoulos syndrome (probands 5 and 6) and one (proband 9) with the mixed syndrome. For this latter twin, two first cousins had idiopathic generalized epilepsies (IGE): one sibling had myoclonic absence epilepsy and his brother had febrile seizures plus and childhood absence epilepsy (Fig. 1).
**Family studies**

Twelve probands (including three twins) had a confirmed family history of epilepsy (Fig. 1); the total number of affected relatives was 24 (one of these was unconfirmed). Of the 24, 20 were first, second or third-degree relatives. With regard to first-degree relatives: 4/24 (16%) parents and 6/22 (27%) siblings were affected.

Generalized epilepsy syndromes occurred in seven relatives: juvenile myoclonic epilepsy (JME), childhood absence epilepsy (CAE), myoclonic absence (MA), generalized tonic clonic seizures alone (GTCA), febrile seizures plus (FS+). Other forms of focal epilepsy occurred in 10 relatives: temporal lobe epilepsy (TLE), rolandic epilepsy (RE), focal motor (FM), occipital (O) and multi-focal epilepsy. Six relatives were unclassified either because they were deceased or their medical records had been destroyed. Epilepsy was unconfirmed in one relative who was deceased and past records had been destroyed.

**Family history of epilepsy according to BOEC syndrome**

Of the five probands with Gastaut syndrome (including two twins), there was a family history of epilepsy in four probands, the total number of affected relatives was eight. Of these: five had focal epilepsies [Gastaut syndrome (2) including a
concordant DZ twin; TLE (2), FM (1), one had IGE (CAE) and two were unclassified.

Of the six probands with Panayiotopoulos syndrome (including three twins), there was a family history of epilepsy in four probands; the total number of affected relatives was six. Of these: two had focal epilepsies [Panayiotopoulos syndrome concordant with the proband (1), TLE (1)], three had IGE [JME (2), GTCA (1)] and one was unclassified.

Of the five probands with mixed syndromes (including two twins), there was a family history of epilepsy in four; the total number of affected relatives was 10. Of these, three had focal epilepsies [O (1), RE (1), multi-focal (1)], three had IGE [MA (1), FS+ and CAE (1), CAE (1)], three were unclassified and another was unconfirmed.

**Febrile seizures**

Two of the 16 probands (probands 12, 16) had a personal history of simple febrile seizures, only one (proband 12) had a family history of febrile seizures in three first cousins. Three (probands 5, 8, 11) had a family history of febrile seizures yet none themselves (Fig. 1).

**Discussion**

**BOEC: a neurobiological spectrum**

Our analysis of 16 probands with BOEC revealed that many individuals do not fit into the classical Panayiotopoulos or Gastaut syndromes but present features of both with a mixed syndrome. The overlap between Panayiotopoulos and Gastaut syndromes observed here, and by previous authors (Gastaut and Zifkin, 1987; Kivity et al., 2000), suggests that the BOEC may be better viewed as a continuum. We suggest that the neurobiological spectrum of BOEC results in Panayiotopoulos syndrome semiology early in childhood and, as the brain matures, the features of Gastaut syndrome become more evident.

Indeed, only some children may be absolutely typical of one or other syndrome. For example, in our cohort of six probands with Panayiotopoulos syndrome, only proband 1 was typical in all respects. Proband 2 and 3 had diurnal seizures which occur in one-third of cases, and proband 3 had a diurnal circling seizure, previously described in Gastaut syndrome (Gastaut, 1982). She was not excluded as circling may be a non-specific feature of occipital seizures. Probands 4 and 5 had brief seizures; whereas, seizures often last minutes to hours in Panayiotopoulos syndrome. Proband 6 later developed seizures consistent with rolandic epilepsy, an evolution previously recognized (Caraballo et al., 2007). Similarly, of the five probands with Gastaut syndrome who had typical, brief, diurnal visual hallucinations, two had rare nocturnal seizures, one of whom also had circling seizures. Moreover, features used to differentiate the syndromes, such as visual hallucinations, may not be evident in the young child who is not able to articulate their aura if present, so absence of an aura may not be a true differentiating marker between Panayiotopoulos and Gastaut syndromes.

Five probands could not be classified as either Panayiotopoulos or Gastaut syndrome because they presented a ‘mixed’ syndrome with features of both (Table 1). For example, seizures were characterized by ictal vomiting, yet were frequent and diurnal (proband 7); or they had rare nocturnal seizures with rare, brief initial visual hallucinations (proband 11).

One historical reason for previously splitting the syndromes related to prognosis, as Gastaut syndrome was considered less benign (Newton and Aicardi, 1983). Contradictory findings suggesting a poor prognosis may be due to inadvertent misdiagnosis of a symptomatic epilepsy in studies that relied on CT imaging whereby MRI visible lesions may have been missed (Newton and Aicardi, 1983; Taylor et al., 2003). Furthermore, symptomatic occipital epilepsies may have the characteristic EEG findings of BOEC and thus EEG cannot be used to discriminate between idiopathic and symptomatic syndromes (Ludwig and Ajmone-Marsan, 1975; Williamson and Spencer, 1986; Barkovich et al., 2001, 2005). In terms of achieving seizure control, the mixed and Gastaut syndromes in our cohort were sometimes harder to control and required two AEDs, yet their long term prognosis was still good, as Gastaut himself emphasized (Gastaut, 1982).

**Genetic studies of BOEC**

Previous studies of the clinical genetics of BOEC have not characterized the seizure disorders in relatives, although BOEC in relatives is rare (Kuzniecky and Rosenblatt, 1987; Nagendrana et al., 1990; Panayiotopoulos, 2002; Lada et al., 2003). Grosso et al. (2008) recently described two families with two members having BOEC of Gastaut type. A family history of epilepsy has been found in 36% of patients with heterogeneous forms of childhood occipital epilepsy (Gastaut, 1985) and in 7% of first-degree relatives of children with Panayiotopoulos syndrome (Ferrie et al., 1997). We sought to explore the clinical genetics of BOEC through twin studies and by characterizing the nature of the epilepsies occurring in relatives of BOEC probands.

**Twins**

Twin studies provide an excellent method for examining the heritability of a disorder. Twin studies in epilepsy show that genetic factors are important with high concordance rates in MZ twin pairs for the idiopathic generalized epilepsies and lower rates for the idiopathic focal epilepsies (Berkovic et al., 1998a). We found a single concordant MZ and DZ twin pair suggesting that genetic factors play a role although, if BOEC were largely genetic in origin, MZ twin pairs would have a significantly higher concordance than DZ pairs. A similar conclusion was recently drawn for the commonest form of idiopathic focal epilepsy, Benign Childhood Epilepsy with Centrotemporal Spikes (BECTS), based on the absence of concordance in 18 twin pairs (Vadlamudi et al., 2004, 2006). As a group, these observations draw into question the premise that the idiopathic focal epilepsies are primarily
genetic disorders. Non-conventional genetic influences such as epigenetic, epistatic or environmental factors are likely to play a role in the aetiology of these disorders (Fraga et al., 2005).

**Family studies**

To explore the clinical genetics of BOEC further, we studied twin pairs and the nature of the family history in probands with a family history of seizure disorders. Our findings show a similar picture amongst the groups of probands with Panayiotopoulos, Gastaut and the mixed syndrome, with relatives having a constellation of partial and generalized syndromes. A family history of BOEC itself was rare.

We cannot comment on familial aggregation in BOEC compared to the general population as our ascertainment was deliberately skewed by electing to study only those probands with a positive family history. For the probands studied, 16% of parents and 27% of siblings had epilepsy. A heterogeneous picture of epilepsy syndromes in family members emerged.

Partial epilepsies, including BOEC as well as other partial epilepsies, were identified in half of the affected family members and generalized epilepsy syndromes in a quarter. The remainder could not be classified. Although there were five relatives with focal epilepsy in the Gastaut group and two in Panayiotopoulos, the numbers of relatives in each subgroup were too small to allow meaningful conclusions regarding differences in family history.

Febrile seizures occur in approximately 16% of children with Panayiotopoulos syndrome (Ferrie et al., 1997; Kivity et al., 2000), although none of our small sample had febrile seizures. Two with the Gastaut syndrome had simple febrile seizures. There was a family history of febrile seizures in 4 of the 16 families, an unsurprising finding as febrile seizures occur between 2% and 4% of children (Verity et al., 1985; Hauser, 1994).

**Overlap of BOEC with other idiopathic epilepsy syndromes**

Children with BOEC show EEG features in common with idiopathic generalized epilepsies and other idiopathic focal epilepsy syndromes. For example, GSW on EEG has been reported in both Panayiotopoulos and Gastaut syndromes (Gastaut, 1982; Panayiotopoulos, 1989a, b; Yalcin et al., 1997) and Caraballo and colleagues noted in their case series that absence seizures may occur concomitantly with BOEC or evolve later (Caraballo et al., 2004) Here, two probands had GSW, only induced by hyperventilation in one, and both had a family history of idiopathic generalized epilepsy. The finding of generalized EEG and seizure phenotypes concomitant with or evolving from BOEC raises the possibility of shared molecular determinants with idiopathic generalized epilepsies.

On the other hand, focal centro-temporal spikes were noted in two probands with Panayiotopoulos and Gastaut syndromes. Another proband with Panayiotopoulos syndrome developed rolandic seizures later. This evolution of idiopathic epilepsy syndromes may be due to age-related expression. Notably, GSW has also been reported in rolandic epilepsy with (Beamanoit et al., 1974) and without clinical absences (Lerman and Kivity, 1975; Bernardina and Beghini, 1976).

Thus, the overlap between idiopathic generalized and idiopathic focal epilepsies occurs at a number of levels, both within individuals as seen in our probands and in the mixed syndromic picture emerging in relatives. It is likely to be due to the complex inheritance that underlies the common idiopathic epilepsies where a number of genes contribute to the aetiology as well as environmental factors. Shared genetic determinants for BOEC and idiopathic generalized epilepsies may raise the risk of both.

Further evidence to support this hypothesis has recently been provided by molecular studies. SCN1A, the gene encoding the alpha subunit of the neuronal type 1 sodium channel, is mutated in generalized epilepsy with febrile seizures plus (GEFS+) and Dravet syndrome (Mulley et al., 2005). In GEFS+, SCN1A missense mutations are found in a small proportion of families with an autosomal dominant pattern of inheritance. The SCN1A gene may be the only gene contributing to the mild phenotype of febrile seizures, and one of several genes contributing to the more severe phenotypes. In GEFS+ families, both generalized and focal epilepsies, including temporal lobe epilepsy, occur (Abou-Khalil et al., 2001; Scheffer et al., 2007). Very recently a family with atypical Panayiotopoulos syndrome has been reported with a SCN1A missense mutation in the proband (Grosso et al., 2007), the mutation was not found in her brother with FS or her parents. This is the first gene to be associated with BOEC; it is interesting that it already has a well-established role in other idiopathic generalized and focal epilepsies. As genes are discovered for BOEC and related disorders, the mechanisms producing such phenotypic heterogeneity will be elucidated.

Considering the patients in this study were selected with the intent of studying the genetics of BOEC, our findings may not necessarily pertain to those subjects without a family history of seizures. Our patients were ascertained because of their family history or twin status and thus cannot be assumed to represent BOEC in the general population. Examination of the phenotypes comprising the Benign Occipital Epilepsies of Childhood in our sample shows that the syndromes described by Panayiotopoulos and Gastaut are less distinct than previously thought with overlap being common. BOEC is best regarded as a neurobiological spectrum with overlapping electro-clinical features, and outcome. Further support for this concept can be drawn from the clinical genetics that show a similar picture of seizure disorders in relatives of children across the spectrum of BOEC, with the caveat that our sample was small. The constellation of partial and generalized phenotypes in families suggests that shared molecular determinants underlie both groups of disorders. The lack of
concordance among MZ twins implies that non-conventional genetic influences such as somatic mutations and epigenetic or environmental factors are also likely to play a role. These observations have implications for diagnosis, genetic counseling and treatment.

Supplementary material
Supplementary material is available at Brain online.

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References


