

# Benign childhood seizure susceptibility syndrome: three case reports

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**ABSTRACT** – In this study, we describe three patients who each had two different forms of idiopathic focal epilepsy. Two of these patients had electroclinical features compatible with Panayiotopoulos syndrome and benign childhood epilepsy with centro-temporal spikes (BCECTS), one of whom developed a particular electroclinical picture of atypical benign focal epilepsy and the other an atypical evolution characterized by verbal auditory agnosia and aphasia. The third patient had clinical and electroencephalographic features of BCECTS and of idiopathic childhood occipital epilepsy (Gastaut type) which evolved into electroclinical features of continuous spikes and waves during slow sleep (CSWS). All three patients presented with two focal idiopathic epilepsies with a particular evolution associated with CSWS, supporting the concept of benign childhood seizure susceptibility syndrome as described by Panayiotopoulos (1993).

**Key words:** continuous spikes and waves, childhood, epilepsy, focal, idiopathic, slow sleep, childhood seizure susceptibility syndrome

The International League against Epilepsy (ILAE) recognizes three well-defined idiopathic focal epilepsies in childhood: the well-known benign childhood epilepsy with centro-temporal spikes (BCECTS), Panayiotopoulos syndrome (PS) which is currently more readily diagnosed, and idiopathic childhood occipital epilepsy of Gastaut (ICOE-G), a less common syndrome (Engel, 2006).

These idiopathic focal epilepsies of childhood are postulated to comprise a group of associated syndromes which form a broad age-related and age-limited benign childhood seizure suscep-

tibility syndrome (BCSSS) with a possible genetic predisposition (Panayiotopoulos, 1993). They share common clinical and EEG characteristics. For a child with BCSSS, the clinical and EEG features of one syndrome may change to those of another syndrome, alternatively a child may present with two different types of benign childhood focal seizures at the same time. Siblings may present with the same benign childhood focal seizures or another type of benign epilepsy. Febrile seizures are common and neuroimaging studies and mental state are typically normal.

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For a small number of these patients, this benign syndrome may evolve into a more aggressive condition with seizures, neuropsychological manifestations, and EEG abnormalities with various combinations and degrees of severity, such as atypical benign focal epilepsy of childhood (ABFE), opercular status epilepticus of BCECTS, Landau-Kleffner syndrome (LKS), and epilepsy with continuous spikes and waves during slow sleep (CSWS) (Fejerman *et al.*, 2000, 2007).

Here, we describe three patients with BCSSS, two of whom had electroclinical features compatible with PS and BCECTS; one developed a particular electroclinical picture of ABFE and the other had an atypical evolution characterized by verbal auditory agnosia and aphasia. The third patient had clinical and electroencephalographic features of BCECTS and ICOE-G which evolved into electroclinical features of CSWS.

## Case report 1

The patient was a 16-year-old right-handed boy, whose parents were in good health and non-consanguineous. His personal and family history were unremarkable.

At three years of age, the boy had a 10-minute episode of eye and head deviation to the right followed by vomiting during nocturnal sleep. The EEG showed left occipital spikes during wakefulness and sleep. Two months later, he had a four-minute episode characterized by anarthria, sialorrhea, and facial clonic seizures during sleep. At the age of four years, he had a brief opercular seizure during sleep. Physical and fundoscopic examinations were normal, no focal neurological signs were found, and routine laboratory investigations, brain CT scan and MRI were normal.

At three years of age, phenobarbital (PHB) was prescribed at 3 mg/kg/day, with blood levels within the therapeutic range. As the patient had repeated seizures, at four years of age PHB was switched to valproic acid (VPA) at 25 mg/kg/day, again with blood levels within the therapeutic range. The interictal EEG recordings during wakefulness and sleep showed left occipital spikes and right centrotemporal spikes, independently.

At the age of five years, he had seizures with similar ictal symptoms and secondary generalisation on awakening. The patient received VPA at a dose of 30 mg/kg/day and carbamazepine (CBZ) at 15 mg/kg/day was added. The interictal EEG recordings during wakefulness and sleep showed left occipital and right centrotemporal spikes. The EEG recording during sleep did not reveal CSWS.

At six years of age, the child began to have frequent atypical absences and negative myoclonus seizures with gait difficulties and learning disturbances. The EEG showed bilateral, asymmetric spikes during wakefulness, and CSWS (*figure 1*). At six and a half years of age, carbamazepine (CBZ) was discontinued and two months later VPA was also discontinued. Clobazam (CLB) was introduced at 0.5 mg/kg/day. After this intervention, the boy remained seizure-free for two and a half years and his motor abilities, learning disturbances, and interictal EEG abnormalities improved.

At eight and a half years of age, he had a brief episode of anarthria and sialorrhea while watching TV. The interictal EEG recording during wakefulness was normal and sleep recording showed bilateral and independent centro-temporal and occipital spikes. At age 10 years, he had four brief seizures, characterized



**Figure 1.** Slow-sleep EEG of Patient 1 shows asymmetric, diffuse continuous spike-and-wave discharges.

by anarthria, and focal facial motor manifestations on different days. All seizures occurred during sleep.

At age 11 years, he was seizure-free with a normal neurological examination and good school performance. The interictal EEG was normal during wakefulness and sleep.

The boy progressed well and at the last control at age 16 years he had remained seizure-free, and neurological examination, cognitive development, and interictal EEG recordings were normal. Since the age of 14 years he has not received any antiepileptic drugs (AEDs).

## Case report 2

The patient was a seven-year-old boy with an unremarkable personal and family history. The pregnancy and delivery, as well as the child's early development, were normal.

At age four years, he had a prolonged seizure characterized by ictal vomiting and left eye and head deviation during sleep. The interictal EEGs during wakefulness and sleep showed bilateral occipital spikes, predominantly on the right side. Neurological examination and routine laboratory studies were normal. Brain CT scan and MRI were normal. CBZ was started at 15 mg/day.

Between the ages of four and six years, the child experienced occasional (every four months) rolandic seizures characterized by anarthria, sialorrhea, and left clonic focal seizures. During one of these episodes, the focal seizure was followed by a generalised tonic-clonic seizure. The interictal EEG recordings during wakefulness and sleep showed independent, right occipital and centrottemporal spikes. CBZ was discontinued and 30/mg/day VPA was instituted. In this period, the repeated EEG recordings during sleep did not show CSWS.

At age six, he progressively developed moderate acquired verbal auditory agnosia with aphasia over a period of three months. Difficulties in comprehension were followed by deficits in expressive language, word-finding difficulties, and phonemic and semantic paraphasias. Non-linguistic cognitive functions were normal. During this period, the patient did not have any type of seizures or behavioural disturbances. The interictal EEG showed frequent bilateral spikes predominantly in the anterior region during wakefulness and CSWS (*figure 2*). Different AEDs, such as 20 mg/day ethosuximide (ETS), 0.5 mg/kg/day CBL, and 18 mg/kg/day sulthiame (STM), were added to VPA treatment, but the language disturbances and CSWS did not change significantly. At six and a half years, AEDs including VPA were discontinued, except for CLB, and oral 1 mg/kg/day prednisone was added. The language and EEG abnormalities started to improve slowly over the course of the next seven months.

Formal language assessment included the Spreen-Benton Battery, the Peabody Picture Vocabulary Test, and the Illinois Test of Psycholinguistic Abilities and confirmed a neuropsychological profile compatible with verbal auditory agnosia and aphasia.

At seven years of age, the child had good language comprehension with mild expressive language disturbances. The interictal EEG during wakefulness showed bilateral centrottemporal spikes with a moderately increased frequency during sleep. The corticosteroids were discontinued and the boy currently receives only CLB at 0.5 mg/kg/day.

At the last control at age seven and a half years, he had remained seizure-free, and neurological examination, cognitive development, and interictal EEG recordings during wakefulness and sleep were normal.

## Case report 3

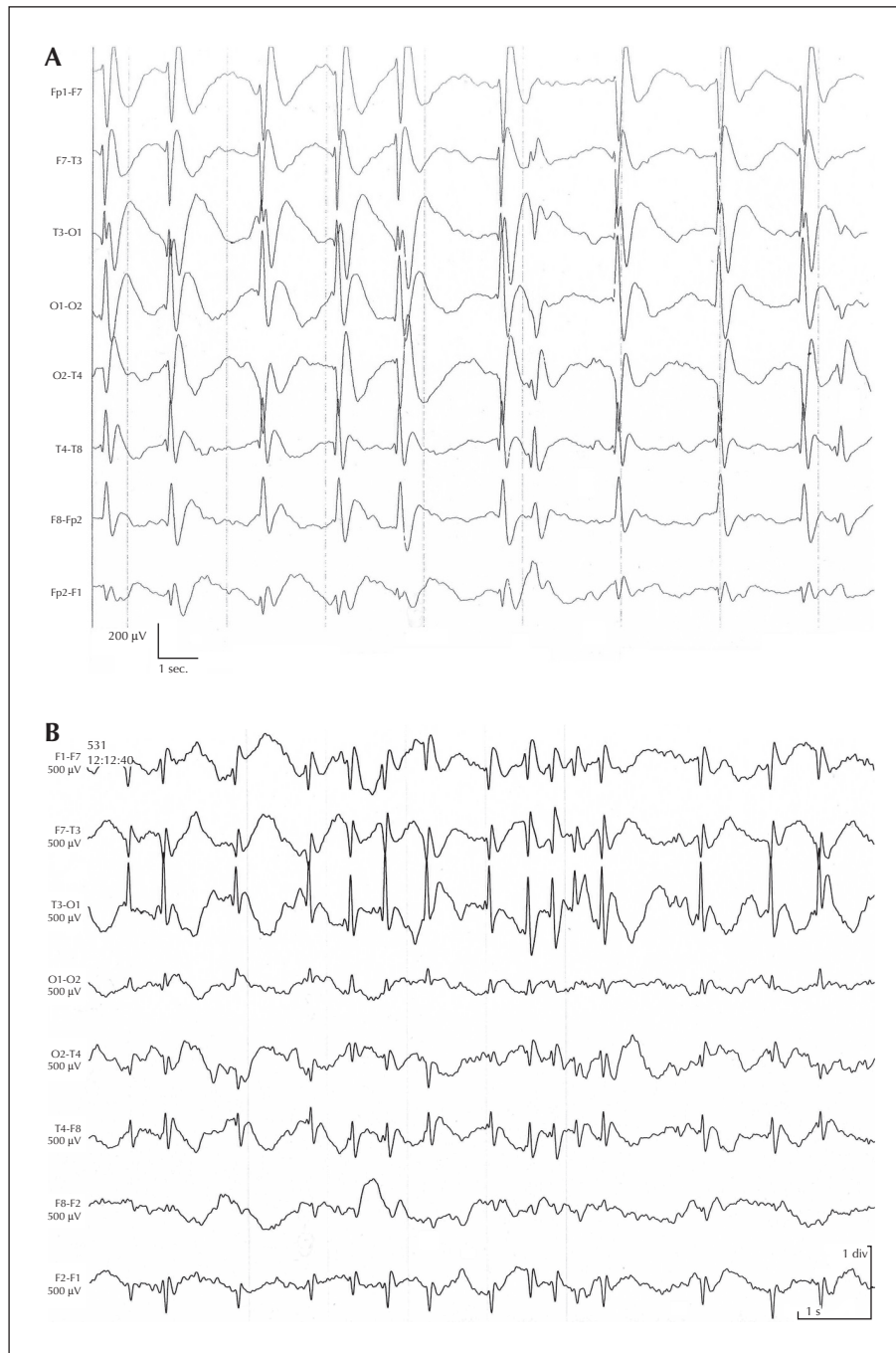
The patient was a seven-year-old girl without significant personal and familial antecedents. Pregnancy and delivery, as well as the child's early development, were normal.

At three and a half years, she presented with a clonic focal seizure during sleep. Interictal EEGs during wakefulness and sleep showed bilateral centrottemporal spikes predominantly on the left side. The EEG recordings during sleep did not show CSWS. Neurological examination and routine laboratory studies, as well as brain CT scan and MRI, were normal. Oxcarbazepine (OXC) at 20 mg/day was started.

Between three and a half and five years of age, the child had monthly rolandic seizures characterized by anarthria, sialorrhea, and right clonic focal seizures, with and without secondary generalisation. The interictal EEG recordings during wakefulness and sleep showed independent, right occipital and bilateral centro-temporal spikes. OXC was discontinued and VPA at 40 mg/kg/day and CLB at 0.5 mg/kg/day were introduced.

At age five years, she had daily visual seizures characterized by brief and multicoloured elementary visual hallucinations, sometimes followed by hemiconvulsions or generalised tonic-clonic seizures. Less frequently, she had deviations of the eyes and migraine-like symptoms. The interictal EEG showed bilateral centro-temporal spikes and bilateral occipital spikes and waves which were reactive to eye closure and opening during wakefulness (*figure 3A*). The EEG recording during sleep showed frequent, bilateral spikes. She continued receiving CLB at the same dose and VPA was replaced by topiramate (TPM) at 5 mg/kg/day.

At age six years, the girl developed gait disturbances, an attention disorder, and hyperkinetic and aggressive behaviour. The gait disturbances were secondary to

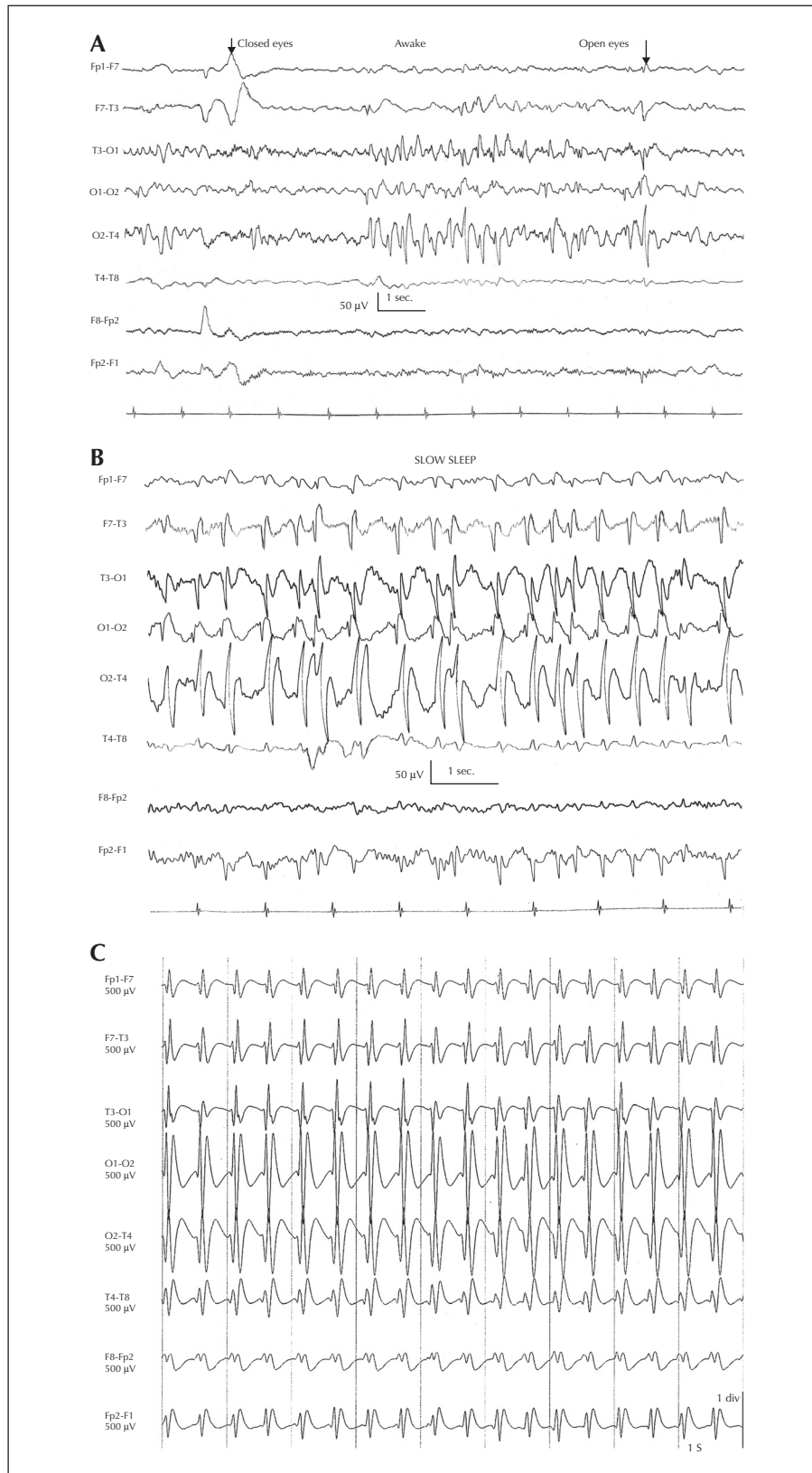


**Figure 2.** EEG of Patient 2. **A)** Slow-sleep EEG shows asymmetric, diffuse high-frequency spike-and-wave activity. **B)** One month later, slow-sleep EEG shows diffuse continuous spike-and-wave discharges.

negative myoclonus. She also had daily, brief focal tonic seizures of the right leg. The interictal EEG recording during wakefulness showed frequent, bilateral spikes and waves predominantly in the posterior region and CSWS (figures 3B, C). TPM was discontinued and sulthiame at 500 mg/day was added. The patient presented with weekly absence seizures and drop-attacks. Her electroclinical picture started to improve slowly in the course of the second semester

of the next year. The Wechsler Intelligence Scale for Children (WISC) was administered showing a borderline IQ.

The girl is currently seven years old and seizure-free. She does not display behaviour disturbances, has a normal neurological examination, and is attending normal school. The interictal EEG during wakefulness shows right temporal and occipital spikes with a moderately increased frequency during sleep.



**Figure 3.** EEG of Patient 3. **A)** EEG during wakefulness shows onset of occipital spike-wave paroxysms after eye closure which disappear after eye opening. **B)** EEG recording during slow sleep shows asymmetric, continuous spikes and waves predominantly in posterior regions. **C)** EEG recording during slow sleep showing diffuse, continuous spikes and waves 15 days later.

## Discussion

We present three patients who each had two different idiopathic focal epilepsies; two had electroclinical features of PS and BCECTS which evolved into ABFE and an atypical evolution characterized by verbal auditory agnosia and aphasia, respectively, and the third had electroclinical features of BCECTS and ICOE-Gastaut which evolved into CSWS. All three patients presented with similar electroclinical features and all had an atypical evolution. These electroclinical findings support the concept of BCSSS as described by Panayiotopoulos (1993). The findings in our three patients may also lead us to suggest that their electroclinical features are consistent with idiopathic focal epilepsies with variable phenotypes, similar to the concept of idiopathic generalised epilepsy with variable phenotypes in adolescence (Engel, 2006).

The slight differences in location of the epileptogenic foci of the benign focal epilepsies presented here are not a justification to consider them as completely separate entities. The fact that often more than one type of benign childhood focal epilepsy occurs in an affected child or siblings, also supports the unified concept of benign childhood focal seizures (Panayiotopoulos, 1993; Caraballo *et al.*, 1998; Lada *et al.*, 2003).

Idiopathic focal epilepsies in childhood are caused by hyperexcitability of a particular functional area or system of the brain; the lower rolandic (somatosensory) cortex that represents the face and the oropharynx bilaterally is involved in BCECTS, the occipital areas (cortical visual system) are involved in ICOE-G, and the central autonomic network is bilaterally and diffusely involved in PS (Panayiotopoulos, 1993; Lada *et al.*, 2003; Koutroumanidis, 2007). However, these conditions are probably related to the same dysfunctional process of brain maturation which is generally mild and reversible and has a genetic predisposition (Panayiotopoulos, 1993).

It is interesting to note that a small number of patients with any type of BCSSS may also suffer typical generalised convulsive or absence seizures either during the active phase of BCSSS or more often at a later stage (Caraballo *et al.*, 2005). Patients with syndromes of idiopathic generalised epilepsies including childhood absence epilepsy may, in sporadic cases, also have EEG focal spikes alone or together with any type of seizure associated with BCSSS (Caraballo *et al.*, 2008).

The particular evolution of the three cases with BCSSS presented here is similar to that of idiopathic focal epilepsies of childhood and may be due to a phenomenon of secondary bilateral synchrony (SBS) which seems to be an age-dependent cause of BCSSS before adolescence (Dalla Bernardina *et al.*, 1989; Kobayashi *et al.*, 1994).

Cases with atypical evolution of BCECTS are widely known and whereas atypical evolution of PS and ICOE-Gastaut is less common, these are also well documented (Fejerman *et al.*, 2000, 2007; Tenenbaum *et al.*, 1997; Caraballo *et al.*, 2001). To our knowledge, our second case report is the first to describe electroclinical features of BCSSS (BCECTS and PS) which progressed to an electroclinical picture similar to LKS, and our third case report is the first to describe electroclinical features of BCECTS and ICOE-G which evolved into CSWS. Thus, we suggest that BCSSS may have an atypical evolution similar to the electroclinical evolution of idiopathic focal epilepsies of childhood (Fejerman *et al.*, 2000, 2007).

The idiopathic focal epilepsies of childhood may be aggressive, manifesting with seizures, neuropsychological symptoms, and different combinations of EEG abnormalities, such as atypical benign focal epilepsy of childhood, opercular status, LKS, epilepsy with CSWS, and mixed forms (Caraballo *et al.*, 1999; Fejerman *et al.*, 2000, 2007; Tassinari *et al.*, 2000).

For our first two patients, the association of CBZ and VPA may have induced CSWS, and in the third patient TPM may have induced atypical evolution. In all three patients, discontinuing the AEDs significantly improved the electroclinical picture. There is evidence that certain AEDs may produce an increase in SW discharge and SBS evolving into CSWS (Corda *et al.*, 2001). This has been demonstrated for older AEDs, such as PHB and phenytoin (Guerrini *et al.*, 1998; Fejerman *et al.*, 2000; Hamano *et al.*, 2002), for CBZ (Shields and Saslow, 1983; Lerman, 1986; Caraballo *et al.*, 1989; Nanba and Maegaki, 1999; Corda *et al.*, 2001; Parmeggiani *et al.*, 2004; Kikumoto *et al.*, 2006), and for VPA (Prats *et al.*, 1998). Of the more recent drugs, anecdotal evidence has been reported for OXC (Hahn *et al.*, 2004; Grosso *et al.*, 2004), lamotrigine (Catania *et al.*, 1999; Cerminara *et al.*, 2004), TPM (Montenegro and Guerreiro, 2002), and levetiracetam (Caraballo *et al.*, 2010). In order to adequately manage treatment in our three cases, AED treatment was firstly discontinued and CLB, ETS, or STM was introduced, either alone or in combination. The first patient responded well to CLB alone, the second patient had a good response to oral corticosteroids, and the third patient responded well to sulthiame.

Our three patients presented with similar electroclinical features. All of them had two different idiopathic focal epilepsies of childhood with a particular evolution associated with CSWS, secondary to SBS. The diagnosis of our patients supports the concept of BCSSS as described by Panayiotopoulos (1993). The electroclinical features of these patients may also indicate a diagnosis of idiopathic focal epilepsies with variable phenotypes. □



**Disclosure.**

None of the authors has any conflict of interest or financial support to disclose.

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