

Self-Limited Focal Epilepsies in Childhood

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Benign focal childhood epilepsies or self-limited focal epilepsies account for approximately one-fifth of all epilepsies in children and adolescents.¹ These syndromes are characterized by age

of onset, specific semiology, genetic predisposition, characteristic EEG morphology, response to antiepileptic medication, and prognosis (Table). On EEG, these seizures manifest as focal epileptiform disturbances without evidence of cortical structural abnormalities. This is in contrast to adult-onset focal epilepsies, in which the chances of finding MRI lesions are higher and seizures are more often refractory to medical treatment.²

This article reviews benign childhood epilepsy with centrotemporal spikes (BECTS); benign occipital epilepsy (BOE), subdivided into early-onset benign childhood occipital epilepsy (Panayiotopoulos type) and late-onset childhood occipital epilepsy (Gastaut type), Landau-Kleffner syndrome (LKS) and epileptic encephalopathy with continuous spike-and-waves in sleep (CSWS). The focus is on recent advances providing increased understanding of etiology, clinical and EEG findings, and management of patients for these epilepsies.

Benign Epilepsy with Centrotemporal Spikes

Previously known as Rolandic epilepsy, which referred to a putative focus at the central sulcus of Rolando in the cerebral cortex,¹ BECTS is a benign epilepsy with centrotem-

poral spikes (Case Study 1). Accounting for 15% to 25% of all childhood epilepsies,³ BECTS is the most common idiopathic childhood epilepsy occurring in children of normal intellect with an age of onset between 3 and 13 years, peak incidence of onset at 7 to 8 years, and resolution by 16 years of age. A predominance has been observed in boys.⁴

Etiology

The genetics of BECTS is still not clearly understood. The hallmark centrotemporal sharp waves are often found in children with BECTS, but are not exclusive to BECTS and occur in more complex epilepsy syndromes (eg. LKS, epileptic encephalopathy with CSWS, atypical benign partial epilepsy, and autism spectrum disorders). The clinical genetics of BECTS is often confused with the genetics of the centrotemporal spike trait. Although centrotemporal spikes are necessary for the diagnosis of BECTS, the genetics of centrotemporal spikes is not the same as that for BECTS

Several investigators have suggested an autosomal dominant inheritance pattern with age-specific inheritance, but most children with these EEG features never experience clinical seizures, suggesting that development of BECTS depends on other genetic and environmental factors.⁵ Researchers have not discovered exactly how the gene produces BECTS. Although multiple genes have been implicated in some families including *BDNF*, *ELP4*, and *GRIN2A*, the majority of children with BECTS do not show a link to an identified gene.⁵ Some

TABLE. FOCAL EPILEPSY SYNDROMES OF CHILDHOOD

Syndrome	Onset	EEG Findings	Prognosis
Benign childhood epilepsy with centrotemporal spikes	Onset: 3-13 y Peak: 7-8 y	Bilateral asynchronous high amplitude, sharp and slow-wave complexes, with horizontal dipole, negative in centrotemporal regions and positive in frontal regions	Remission by adolescence
Landau-Kleffner syndrome	Onset: 3-10 y	Continuous diffuse slow spikes and waves at 1.5-2.5 Hz occurring at all slow-sleep stages	Remission by adolescence
Continuous spike-and-wave during sleep (CSWS)	Onset: 2-4 y	Infrequent spikes and waves; continuous diffuse slow spikes and waves at 1.5-2.5 Hz occurring at all slow-sleep stages, electrical status epilepticus in sleep (ESES)	Poor prognosis with long duration of ESES
Panayiotopoulos syndrome	Onset: 1-14 y Peak: 3-6 y	Interictal EEG with occipital spikes and multifocal, high amplitude, sharp slow wave complexes	Remission approximately 3 years after onset.
Gastaut Type	Peak: 8 y	Bilateral occipital spike-wave discharges that activate with eye closure and diminish upon eye opening	Remission chance of 50-60% about 2-3 y after onset.

Case Study 1

A previously healthy boy, age 8 years, presented with a first unprovoked seizure that began in the early morning and lasted 2 minutes. He was born with no perinatal problems and had normal neurocognitive development. There was no family history of epilepsy. His parents were alerted to his seizure by his older sibling and then found him in bed, with his face turned to the right, staring with his “tongue stuck,” salivating, gurgling, with the left side of his face twitching. He recovered consciousness and, by the time emergency services arrived, was able to answer questions and walk to the ambulance. His neurologic examination findings were normal including routine blood tests and a head CT. He was referred to the neurology clinic, and EEG was performed 2 days later with the results shown in Figure 1.



Figure 1. EEG in benign epilepsy with centrotemporal spikes showing activation of spike-wave clusters in early sleep over the central temporal regions.

studies have found positive evidence of linkage on band 14 of the long arm of chromosome 15 (15q14) and either the gene encoding for the AChR α -7 subunit or another closely linked gene may be responsible for some, but not all, cases of BECTS. Overall evidence suggests BECTS is genetically heterogeneous.⁶

Clinical and EEG Features

The first seizure is typically a generalized tonic-clonic seizure during sleep. In BECTS, the seizure focus originates from the lower portion of the perirolandic region in the upper sylvian bank.¹ Consciousness is most often unimpaired initially. Approximately 15% of children with BECTS have seizures both in sleep and wakefulness, whereas 20% to 30% of children with BECTS have seizures only while awake.⁴

An appropriate seizure semiology is crucial for a correct diagnosis. The classic features involve the lower face unilaterally with paresthesias of the tongue, lips, gums, and cheek;

clonic or tonic activity of the face, lips, and tongue; dysarthria; and drooling.¹ Very young children with BECTS may also present with hemiconvulsions instead of the typical facial seizure.⁶ Progression to hemiconvulsions occurs in approximately 50% of children with BECTS; these may be followed by postictal Todd's hemiparesis.¹ Todd's hemiparesis is a postictal paralysis, most often of an arm, reported to occur in 7% to 16% of children with BECTS that suggests focal onset in patients who present with an apparently generalized seizure.⁷

In most children with BECTS, seizures last from a few seconds to several minutes; some children present with atypical features including status epilepticus, developmental delay, daytime-only seizures, screaming as a seizure component, and postictal Todd's hemiparesis.⁸ Although most of these children ultimately have remission of their epilepsy, many are left with varying degrees of cognitive disabilities.⁹

In typical patients with BECTS, the interictal EEG shows high amplitude, sharp and slow-wave complexes, characteristic horizontal dipole with maximum negativity in centrotemporal regions, and positivity in frontal regions followed by slow waves. These occur bilaterally and often asynchronously. Discharges frequently cluster and are enhanced in drowsiness and non-rapid eye movement (NREM) sleep.¹⁰ Unique features like ictal spike-and-wave discharges may show dipole reversal, with electropositivity in the centrotemporal region and negativity in the frontal area.

Treatment and Prognosis

Decisions regarding initiation of treatment in BECTS depend on whether children can undergo the natural course of the disease versus the efficacy and risks of treatment. Unfortunately, data available on the natural course of BECTS are scarce. Children with BECTS may not require antiepileptic drugs (AEDs); if seizures are frequent or there are secondarily generalized tonic-clonic seizures, daytime seizures, or comorbid conditions, AEDs may be required.

Common medications used include carbamazepine, oxcarbazepine, levetiracetam, gabapentin, topiramate, and lamotrigine (see *Choosing Antiepileptic Drugs* in this issue). Supporting evidence to validate the use of specific antiepileptic drugs for BECTS is limited despite widespread variation in practice.¹¹

Traditionally BECTS has been considered a benign disorder without long-term consequences. Long-term follow-up studies confirmed that more than 90% of patients achieve remission by age 12 years. This prognosis was considered favorable even for patients whose seizures are difficult to control because seizures almost always remit spontaneously in adolescence.¹¹

Recent studies have now found that patients with BECTS may have a variety of cognitive disturbances including language impairment, memory dysfunction, and auditory processing difficulties. These cognitive impairments are not linked to seizure-related factors, such as seizure frequency, time since

the last seizure, or laterality of the electrical focus.¹² Some studies have demonstrated that these patients' full-scale IQ is within the normal range, but lower scores have been noted on language-related tasks, some executive functions, attention, memory, auditory and verbal learning tasks, and a variety of behavioral and emotional difficulties.¹³ Thus the term benign is increasingly being challenged, and the International League Against Epilepsy (ILAE) suggests the term self-limited and pharmacoresponsive.¹⁴

Landau-Kleffner Syndrome

Landau-Kleffner syndrome is an atypical BECTS phenotype with acquired epileptic aphasia typically developing in healthy children who acutely or progressively lose receptive and expressive language with the appearance of paroxysmal EEG changes. This syndrome is often associated with 2 other symptoms: behavioral problems and epileptic seizures. The ILAE defines this syndrome as a childhood disorder in which an acquired aphasia, multifocal spikes, and spike-and-wave discharges are associated. The age of onset ranges from 3 to 10 years in children with previously normal cognitive and language development. The male-to-female ratio is 2:1.¹⁵

Etiology

The etiology of LKS is largely unknown. Many hypotheses have been proposed including genetic predisposition, autoimmune mechanisms, cerebral arteritis, toxoplasmosis, neurocysticercosis, low-grade brain tumors, and demyelinating disease.¹⁶ In recent studies, a de novo missense mutation in *GRIN2A* was identified in a patient with LKS, and it was concluded that the mutant decreased *N*-methyl-D-aspartate (NMDA) receptor activation suggesting NMDAR hypofunction may contribute to the pathogenesis of LKS.¹⁶

Clinical and EEG Features

Children with LKS initially present with auditory-verbal agnosia in the form of loss of receptive language, at a stage that makes parents complain of deafness. This is followed by a loss of expressive speech and behavioral disturbances.⁴

The EEG findings in LKS are characterized by continuous diffuse slow spikes and waves at 1.5 to 2.5 Hz occurring at all slow-sleep stages. This pattern is called electric status epilepticus in sleep (ESES) and appears to have a lateralization in epileptiform activity that correlates with language impairment.¹⁵ The interictal epileptiform discharges are mainly localized in the temporoparietal-occipital lobes.⁴

Treatment and Prognosis

Antiepileptic drugs like valproate, ethosuximide, clonazepam, or clobazam can control the seizures (see *Choosing Antiepileptic Drugs* in this issue). Carbamazepine, oxcarbazepine, topiramate, and lamotrigine are avoided because of

known exacerbation of epileptiform discharges.⁴

Corticosteroids have been associated with an improvement in evolution of the disease.¹⁵ Intravenous immunoglobulin (IVIg) used as monotherapy has demonstrated promising results in some studies.¹⁷ When a patient's seizures are refractory to medical treatment, subpial transection surgery may be effective.¹¹

Most patients with LKS become seizure free with antiepileptic drugs, and EEG abnormalities and seizure episodes decrease by the time most patients reach age 15 years.¹⁸ The prognosis for language impairment can have lasting effects and range from severe persistent aphasia to complete recovery in adult life. Starting speech therapy, sign language, and special education as early as possible is beneficial for children with LKS.¹¹

Continuous Spike-and-Waves during Sleep

Epileptic encephalopathy with CSWS is an epileptic encephalopathy that affects children and adolescents and is more predominant in boys than girls.¹⁹ The age of onset has a bimodal distribution from age 2 to 4 years. Seizures that occur around 2 years of age can be attributed to underlying structural brain lesions, whereas seizures that occur around age 4 have an unknown etiology. The prodromal seizure activity is thought to be easier to control with minimal effects on brain development. The acute stage occurs around age 5 to 6 years when EEG abnormalities are seen and developmental regression occurs. Seizure freedom occurs at approximately 6 to 9 years of age.⁴ Epileptic encephalopathy with CSWS is characterized by ESES.¹⁹

Etiology

The etiologies of CSWS range from unknown etiology to studies that demonstrate structural brain abnormalities to long-standing thalamic lesions.²⁰ EEG recordings demonstrate that the thalamus along with the mesial temporal and parietal regions may precipitate the development of spike-and-wave discharges.²¹ Genetic mutations like *GRIN2A* pathogenic variants can also play a role and account for 17.6% of CSWS.²²

Clinical and EEG Features

The clinical presentation of CSWS consists of a global regression comprising behavioral, cognitive, language, social, and motor deficits.¹¹ There are 4 stages: dormant, prodromal, acute, and residual. Seizures begin to appear around 2 years of age in the prodromal stage and range from simple focal motor, complex focal, absence, or myoclonic, usually occurring at night. The EEG findings are not distinct and may represent infrequent spikes and waves. As the disease progresses to the acute stage, seizures occur more frequently and still predominantly at night. The characteristic features of these acute-stage seizures range from hemiconvulsive, gen-

eralized tonic-clonic seizures (GTCS), absence seizures, drop attacks, and convulsive or nonconvulsive status epilepticus. The EEG displays an ESES pattern (Figure 2), and during this stage patients suffer a global and severe regression.^{11,23}

Treatment and Prognosis

The goal of treatment for patients with CSWS is to control the clinical seizures. Useful AEDs include benzodiazepines, valproate, ethosuximide, levetiracetam, and corticosteroids.¹¹ Despite disappearance of clinical seizures and EEG abnormalities in patients with CSWS, the prognosis depends on the etiology and duration of active epilepsy. The longer the duration of ESES, the worse the outcome is likely to be.

Early-Onset Benign Childhood Occipital Epilepsy: Panayiotopoulos Syndrome

Early-onset childhood occipital epilepsy known as Panayiotopoulos syndrome is a common childhood epilepsy, accounting for approximately 6% of children with epilepsy (Case Study 2). The age of onset is as early as age 1 year with a peak incidence of onset at age 3 to 6 years, and most patients have no neurodevelopmental disorders.¹⁰ There is a triad of clinical symptoms: nocturnal seizures, tonic eye deviation, and vomiting.¹¹ Autonomic symptoms are prominent.²⁴ Girls and boys are equally affected, and in two-thirds of patients, Panayiotopoulos syndrome mainly occurs in sleep.¹¹

Etiology

Panayiotopoulos syndrome results from multifocal cortical hyperexcitability and an unstable autonomic system.¹⁰ No causal gene has been identified, although approximately 10% of those affected have a family history of similar seizures, and approximately 17% have a high prevalence of febrile seizures.⁴ The neuroanatomical and neurophysiological causes of the autonomic symptoms are unknown. Perinatal hypoxia/ischemia, hypoglycemia, inborn errors of metabolism, and intracranial bleeding resulting in occipital

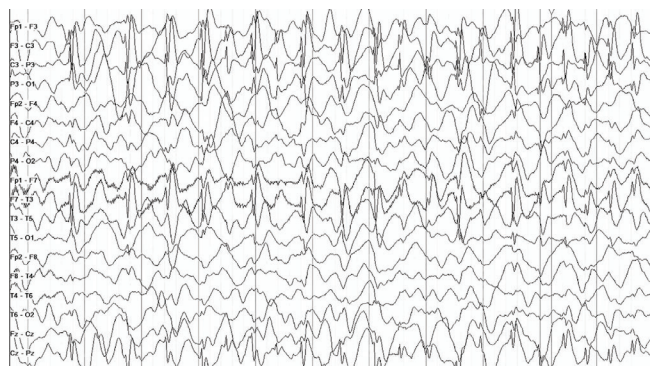


Figure 2. EEG in continuous spike-and-waves epilepsy during sleep. Note the continuous focal spike-and-wave activity in slow-wave sleep, distributed over the left central temporal regions.

▶▶▶ Case Study 2

A girl, age 4 years, with normal development and no past medical problems was found waking up from sleep as if in a dream multiple times during the past month. Her parents reported that during these episodes, she had no fever, had profuse sweating, dilated pupils initially, and was unresponsive to stimulation, after which she would start vomiting. When her parents could not get her to respond even after 20 minutes, she was brought to the emergency department. Her vital signs and the findings of her blood counts, metabolic panel, urinalysis, drug screen, and eosinophil sedimentation rate (ESR) were within normal limits. Her physical examination findings were unremarkable. There were no focal neurologic deficits or signs of meningitis or increased intracranial pressure. She was unresponsive to stimulation, floppy, and staring for 2 minutes. She was admitted to the hospital for observation. A brain MRI with and without contrast had normal findings. The EEG is shown in Figure 3.



Figure 3. EEG in benign occipital epilepsy. Note the spike-wave discharges that are more visible on the left.

brain damage have been recently speculated as possible causes of Panayiotopoulos syndrome.²⁵

Clinical and EEG Features

Patients with Panayiotopoulos syndrome commonly present with autonomic symptoms including recurrent vomiting; seizure onset is during sleep. Additional autonomic symptoms include pallor, incontinence, hypersalivation, cyanosis, mydriasis, coughing, breathing, and cardiac abnormalities and rarely syncope.⁵ Seizure events can last anywhere from 5 minutes to several hours, with one-third of patients developing focal status epilepticus. Longer seizures are common in sleep as well as during wakefulness.⁴

Interictal EEG findings show mainly multifocal, high-amplitude, sharp slow-wave complexes appearing in variable

locations that often shift regions on subsequent recordings.⁷ Occipital spikes are mostly involved.⁷

Treatment and Prognosis

Panayiotopoulos syndrome has an excellent prognosis. Children with an increased number of seizures tend to achieve long-term remission⁴ with no lasting effects of the syndrome. Disease duration is approximately 3 years.²⁶ Use of specific AEDs is not required. Children with prolonged seizures have been intermittently treated with benzodiazepines.⁴

Late-Onset Benign Childhood Occipital Epilepsy

Late-onset benign childhood occipital epilepsy (BOE), termed Gastaut type, is a benign epilepsy that begins later in childhood with a peak incidence of onset at 8 years of age.⁴ Gastaut-type epilepsy is a relatively rare form of occipital epilepsy with an occurrence rate of 2% to 7% of benign childhood epilepsies. Both sexes are equally affected.¹ Gastaut type epilepsy is characterized by brief seizures with mainly elementary visual symptoms followed by hemiconic seizures during wakefulness.¹

Etiology

Gastaut type BOE has an increased prevalence in patients with a family history of epilepsies or migraine.¹ The epileptogenic zone lies within the occipital lobes.

Clinical and EEG Features

Initially, children present with elementary visual hallucinations. These are brief and described as multicolored circular-looking patterns appearing in the visual field.¹¹ The second most common symptom is sudden transient ictal blindness. The most common nonvisual ictal symptom is turning of the head occurring in 70% of cases.¹ Consciousness is usually intact during the visual symptoms.⁴ Migraine-like postictal headaches occur in some patients.¹

The EEG shows bilateral occipital spike-wave discharges that activate with eye closure and diminish upon eye opening; this is referred to as fixation-off phenomenon.¹⁹ Random occipital spikes during sleep are frequent in some patients.¹¹

Treatment and Prognosis

Children with BOE Gastaut type often suffer from frequent seizures and therefore medical treatment is mandatory. Carbamazepine use has shown to dramatically reduce or stop seizures within days of appropriate treatment.¹¹ Prognosis is generally favorable. Remission occurs in 50% to 60% of children within 2 to 3 years of onset.

Summary

Focal epilepsy syndromes in childhood are associated with a favorable prognosis and age-related resolution is typical.

The semiology and EEG features are characteristic for each syndrome and genetic etiologies are suspected but not fully elucidated. Unlike adult focal epilepsy, which is often related to a focal lesion in children, there are no focal structural brain abnormalities present. Several of these conditions have been referred to or even named as benign syndromes; a recent position paper from the ILAE task force¹⁴ discourages the use of the term and instead suggests the terms self-limited or pharmacoresponsive as appropriate. Treatment includes AEDs for severe cases or observing the natural course of illness in mild cases. ■

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