Continuous Spike and Waves During Sleep and Electrical Status Epilepticus in Sleep

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Abstract: Continuous spike and waves during sleep is an age-related epileptic encephalopathy that presents with neurocognitive regression, seizures, and an EEG pattern of electrical status epilepticus during sleep. Patients usually present around 5 years of age with infrequent nocturnal unilateral motor seizures that progress within 1 to 2 years to a severe epileptic encephalopathy with frequent seizures of different types, marked neurocognitive regression, and an almost continuous spike-wave EEG pattern during slow-wave sleep. The pathophysiology of continuous spike and waves during sleep is not completely understood, but the corticothalamic neuronal network involved in physiologic oscillating patterns of sleep is thought to be switched into a pathologic discharging mode. Early developmental injury and/or genetic predisposition may play a role in the potentiation of age-related hyperexcitability in the immature brain. A better understanding of the mechanisms leading to electrical status epilepticus during sleep may provide additional therapeutic targets that can improve the outcome of seizures, EEG pattern, and cognitive development in patients with continuous spike and waves during sleep.

Key Words: Electroencephalography, Seizures, Epilepsy, Thalamus, Epileptic networks, Developmental regression.

(J Clin Neurophysiol 2011;28: 000 –000)

HISTORY AND TERMINOLOGY

In 1971, Tassinari’s group reported an EEG pattern of continuous spikes and waves during slow-wave sleep in six children. This EEG pattern occurred without any clinical signs, and therefore the condition was described with terms such as “electrical” or “subclinical” (Patry et al., 1971). Since then, electrical status epilepticus during sleep (ESSES) was the widely used acronym to describe this EEG pattern of generalized spiking during non-rapid eye movement (REM) sleep.

All patients in the original series had moderate to severe cognitive dysfunction and five of the six patients had epileptic seizures (Patry et al., 1971). As more cases were published, it became clear that electrical status epilepticus during non-REM sleep occurred at the time of severe neurocognitive deterioration (Dalla Bernardina et al., 1978; Kellermann, 1978; Laurette and Arfel, 1976). The term ESSES was considered inaccurate because an EEG pattern alone—without detectable seizures in some patients—should not define “status epilepticus.” More importantly, the acronym “ESSES” only described the EEG pattern and not the associated neuropsychological regression. Therefore, some authors modified the abbreviation ESES to “Encephalopathy with Status Epilepticus during Sleep” in an attempt to reflect the clinical findings and merge clinical and EEG features to a syndromatic presentation (Tassinari et al., 2000, 2005, 2009). Subsequently, the International League Against Epilepsy (ILAE) adopted the term “Continuous Spike and Waves during Sleep” (CSWS) as an epilepsy syndrome and defined it as follows: “Epilepsies with continuous spike-waves during slow-wave sleep results from the association of various seizure types, partial or generalized, occurring during sleep, and atypical absences when awake. Tonic seizures do not occur. The characteristic EEG pattern consists of continuous diffuse spike-waves during slow-wave sleep, which is noted after onset of seizures. Duration varies from months to years. Despite the usually benign evolution of seizures, prognosis is guarded because of the appearance of neuropsychological disorders” (Commission on Classification and Terminology of the International League Against Epilepsy, 1989). In recent reports of the Commission on Classification and Terminology of the International League Against Epilepsy, “Epileptic encephalopathy with continuous spike and wave during sleep” (CSWS) was used (Berg et al., 2010; Engel, 2006).

Although differently named and described by various authors, two key characteristics of this syndrome are unequivocal: a clinical component of motor, cognitive, behavioral, and/or language deterioration from baseline in a previously cognitively normal or delayed child, and an EEG component of usually generalized (near)-continuous spike and wave complexes during a significant proportion of non-REM sleep.

Many authors use ESSES and CSWS as interchangeable terms. In this article, we chose to refer to the electrographic pattern as ESSES, whereas the clinical syndrome consisting of regression, epilepsy, and ESSES EEG pattern will be referred to as CSWS.

EPIDEMIOLOGY

Continuous spike and waves during sleep is an age-dependent syndrome occurring only in children. Data on epidemiology are scarce and difficult to assess in part because of variable definitions and inclusion criteria. It is considered rare and represents approximately 0.5% to 0.6% of all childhood epilepsy cases seen at tertiary epilepsy centers (Eksioğlu et al., 2009; Morikawa et al., 1989), and this number may represent a considerable referral bias. In a recent series of 415 patients undergoing epilepsy surgery, 2% of patients had an ESSES pattern (Loddenkemper et al., 2009b). There may be a slight male preponderance (~60% males) when data are pooled from different series (Bureau, 1995b; Inutsuka et al., 2006; Kelemen et al., 2006; Ohtsuka et al., 2002; Van Hirtum-Das et al., 2006; Wang et al., 2008; Yan Liu and Wong, 2000).

CLINICAL PRESENTATION

The classic clinical presentation consists of a child around 5 years old who presents with new-onset seizures and mild develop-
mental problems or mild regression. The age of clinical onset peaks around 4 to 7 years. It rarely begins after 12 years (Bureau, 1995a, 1995b), and onset during the first 2 years of life has been described (Guzetta et al., 2005; Inutsuka et al., 2006; Ohtsuka et al., 2002).

Seizures
Seizures are the presenting symptom in around 80% of the cases and the first seizure peaks around 3 to 5 years. Initial seizures occur typically out of sleep. They present with unilateral (50% of cases) clonic or tonic–clonic features and lead to hemiconic status epilepticus in 6% of cases. Other frequent seizure types at presentation include absence seizures, simple and complex partial seizures, and (secondary) generalized clonic or tonic–clonic seizures. At the time of onset, two or more seizure types are seen in only 20% of patients (Bureau, 1995b). Daily or more frequent seizures are initially rare and also occur in <20% of cases (Bureau, 1995b). When the ESES pattern appears, lateralizing and localizing features decrease during seizures and there is no occurrence of seizures, atonic, and astatic seizures. At this stage, approximately 60% of cases have several seizure types and 70% of cases suffer several seizures per day (Bureau, 1995a, 1995b; Morikawa et al., 1995; Sarco and Takeoka, 2009).

Neuropsychological regression and ESES on EEG appear 2 to 3 years after seizure onset, approximately around 7 years of age (Bureau, 1995b; Morikawa et al., 1995). Neuropsychological deficits are the reported presenting symptom in approximately 20% of patients. The ESES pattern is rarely picked up as the sole presenting symptom (Bureau, 1995b).

Neuropsychological Presentation
The neuropsychological deterioration involves a wide spectrum of developmental and neurocognitive milestones, in varying but often severe degrees. Decrease in overall intelligence quotient, language deterioration in the form of a fluctuating aphasic disorder, hyperactive and impulsive behavior, and learning disorders are frequently reported. Impairment in temporospatial orientation, memory problems, reduced attention span, aggressive or compulsive behavior, poor interpersonal contact, emotional liability, disinhibition, and even a psychotic-like condition have been described (Bureau, 1995a; Morikawa et al., 1995; Sarco and Takeoka, 2009; Tassinari et al., 2000). Fine and gross motor skills may also be affected (Tassinari et al., 2000, 2005; Van Hirtum-Das et al., 2006), and dystonia, dyspraxia, ataxia, unilateral motor deficits, and negative myoclonus are frequently considered as most disabling (Tassinari et al., 2000).

Classification
Although the above-mentioned characteristics include the defining features of the syndrome, many cases of CSWS are atypical. A patient-oriented terminology, describing several dimensions of the condition including localization, seizure semiology and frequency, causative agents, and the associated conditions in every individual (Berg et al., 2010; Loddenkemper et al., 2005) may provide further clinical information than an attempt to fit epileptic patients into ultimately variable diagnostic syndromic categories (Kellinghaus et al., 2004; Manford et al., 1992).

EEG FINDINGS AND EEG CRITERIA FOR DEFINING ESES

Definition of the ESES Pattern
The following features are usually shared by most publications on ESES:

1. Activation or potentiation of epileptiform discharges in sleep (Bureau, 1995a; Guzzetta et al., 2005; Scheltens-de Boer, 2009; Tassinari et al., 2000).
2. (Near)-continuous, bilateral, or occasionally lateralized slow spikes and waves (Bureau, 1995a; Commission on Classification and Terminology of the International League Against Epilepsy, 1989; Tassinari et al., 2000).
3. Occurrence "during a significant proportion" of the non-REM sleep with a threshold ranging from >25% to >85% (Bureau, 1995a; Boel and Casaer, 1989; Bureau, 1995a; Dalla Bernardina et al., 1978; Hirsch et al., 1990; Inutsuka et al., 2006; Laurette and Arfel, 1976; Loddenkemper et al., 2009b; Patry et al., 1971; Saltik et al., 2005; Tassinari et al., 2000, 2005; Van Hirtum-Das et al., 2006; Yan Liu and Wong, 2000; Yasuhara et al., 1991).

Spike-Wave Index Assessment
The spike-wave index (SWI) quantifies the frequency of spiking in the EEG tracing. Most authors loosely refer to this term as the percentage of non-REM sleep occupied by spike waves, without defining the exact method for calculating it (Inutsuka et al., 2006; Tassinari et al., 2000, 2005; Saltik et al., 2005). Others define the SWI as the percentage of 1-second bins with at least one spike and wave relative to the total 1-second bins in non-REM sleep (Aebi et al., 2005; Tas et al., 2009). The SWI is higher in the first sleep cycles, and progressively decreases through the night (Bureau, 1995a). Atypical EEG features include marked interhemispheric asymmetry, which in its most extreme presentation can present as unilateral spike and waves (Bureau, 1995a; Eksioglu et al., 2009). In our own experience, the spike frequency count expressed as the number of spikes per time interval may actually be more sensitive to changes in the EEG epileptiform activity than the SWI (Sánchez Fernández et al., in preparation) and sleep stage confirmation as well as computer-based spike counts may help increase objectivity (Chavakula et al., 2009). Spike frequency during wakefulness and sleep can be compared, and a potentiation factor could be calculated (Sánchez Fernández et al., in preparation). The evolution of the SWI activity within the same patient, expressed as the number of spikes per time interval, may be clinically more useful than a static SWI threshold for all patients (Sánchez Fernández et al., in preparation).

Localization of EEG Findings
During wakefulness, the most frequent locations of epileptiform discharges are frontotemporal or centrottemporal. In some cases, focal and generalized spike-wave complexes partially overlap. During sleep, focal epileptiform discharges disseminate, and spiking becomes more frequent, widespread, and ultimately generalized, frequently with a frontal or central maximum.

Frequency of Spiking
The ESES pattern usually consists of a (near)-continuous usually generalized and symmetric spike-wave pattern with a variable frequency of discharges, typically in the 1.5 to 3 Hz range. Tassinari’s group suggested that at least 85% of non-REM sleep should be occupied by generalized spike-wave activity for the diagnosis of CSWS (Patry et al., 1971; Tassinari et al., 2000, 2005). This group also suggested assessment with three different EEGs over a period of at least 1 month (Patry et al., 1971; Tassinari et al., 2000, 2005). Although some authors (Boel and Casaer, 1989; Dalla Bernardina et al., 1978; Hirsch et al., 1990; Laurette and Arfel, 1976; Loddenkemper et al., 2009b; Saltik et al., 2005; Tassinari et al., 2000; Yan Liu and Wong, 2000; Yasuhara et al., 1991) use the classic definition of (near)-continuous spike-wave discharges during non-REM sleep for the diagnosis of CSWS, others set the SWI threshold at different percentage levels. For example, in a series of
15 patients with ESES pattern (Inutsuka et al., 2006), an SWI of at least 60% was required to meet the diagnosis; a case report (Kobayashi et al., 2006) considered an EEG with an SWI of 41.4% compatible with CSWS, and a series of 102 children with sleep-activated spikes and waves (Van Hirtum-Das et al., 2006) considered an SWI of 25% or more as an inclusion criterion. Others have also included sleep-potentiated spiking as “sleep overactivation pattern” (Guzzetta et al., 2005), or “near-ESES” (Saltik et al., 2005) referring to patients electroclinically highly suspected for CSWS, but with an SWI below the 85% threshold. The ILAE criteria do not provide a cutoff value and only require “continuous diffuse spike waves during slow-wave sleep” (Commission on Classification and Terminology of the International League Against Epilepsy, 1989). To prevent overdiagnosis, sleep potentiation of epileptiform activity and seizures seen in other epilepsy types should be taken into account (Bazil and Walczak, 1997; Janz, 1962; Kotagal, 2001; Kotagal and Yardi, 2008; Malow et al., 1998; Quigg, 2000; Touchon et al., 1991).

**ESES and Sleep**

Epileptiform discharges appear as soon as the patient falls asleep and persist throughout non-REM sleep (Bureau, 1995a; Tassinari et al., 2000). Sleep stages 1 and 3 are difficult to differentiate because defining sleep features are either missing or intermingled with the (near)-continuous epileptiform activity of ESES. REM sleep is easily recognized by the disappearance of the ESES pattern and the presence of rare bursts of spikes seen during wakefulness (Bureau, 1995a; Tassinari et al., 2000).

**Course of EEG Findings**

At CSWS onset, the interictal EEG during wakefulness shows infrequent focal or multifocal spikes, slow waves or spike waves, sometimes in bursts. Non-REM sleep potentiation of interictal epileptiform discharges occurs even early in the course of the disease (Bureau, 1995a; Tassinari et al., 2000). Around the time of neurocognitive regression and increase in seizure frequency, interictal abnormalities also become more prominent during wakefulness (Fig. 1A) and the ESES tracing appears during non-REM sleep (Fig. 1B).

**ETIOLOGY AND NEUROIMAGING FINDINGS**

Although many (62%–74%) patients reportedly have normal neuropsychological and motor function before the onset of ESES (Morikawa et al., 1989; Tassinari et al., 1992), associated structural defects (Buzatu et al., 2009; Guerrini et al., 1998; Guzzetta et al., 2005; Ohtsuka et al., 2002; Van Hirtum-Das et al., 2006) have been seen in up to 33 of 56 (59%) (Van Hirtum-Das et al., 2006) and 18 of 40 (45%) cases (Buzatu et al., 2009). A lower proportion, 44 of
147 (30%), was found in a series that included all patients with sleep-potentiated interictal spikes (Tas et al., 2009).

The types of structural abnormalities associated with CSWS are heterogeneous. They frequently consist of early developmental lesions: perinatal vascular lesions and related conditions (21%–78%), cortical malformations (23%–25%), abnormal/delayed myelination (9%–15%), and others (Buzatu et al., 2009; Tas et al., 2009; Van Hirtum-Das et al., 2006) (Table 1). Rare cases have also been associated with neurodegenerative disorders (Couetelier et al., 2008; Kobayashi et al., 2006) and the use of topiramate (Montenegro and Guerreiro, 2002). Therefore, CSWS is likely an age-specific response to diverse neurologic insults in predisposed children (Guzzetta et al., 2005; Ohtsuka et al., 2002; Rudolf et al., 2009; Tassinari et al., 2000; Van Hirtum-Das et al., 2006).

OUTCOME AND PROGNOSIS

Recent attempts to outline the prognosis of CSWS focus on three major outcome parameters: seizure frequency and severity, EEG pattern, and neurocognitive function.

Seizures

Clinical seizures tend to remit spontaneously around puberty. This pattern is independent of the etiological lesion, as illustrated by the universal age-related remission, even in patients with a static cortical malformation (Guerrini et al., 1998; Guzzetta et al., 2005; Ohtsuka et al., 2002), or a progressive neurodegenerative disease (Kobayashi et al., 2006).

EEG Pattern

Electrical status epilepticus during sleep is an eventually self-limiting EEG pattern that uniformly disappears around the age of 11 years, approximately 3 to 4 years after its onset (Morikawa et al., 1995). Subsequently, the EEG tracing can be normal or, less frequently, show more focal discharges that tend to disappear after a variable period of time (Bureau, 1995a; Morikawa et al., 1995). The resolution of clinical seizures may precede, coincide with, or follow the resolution of the ESES pattern, and each of these situations occurs, approximately, in one third of the cases (Bureau, 1995a).

Neurocognitive Function

The resolution of the EEG pattern and epileptic syndrome around puberty is associated with neurocognitive and behavioral improvement. However, most patients demonstrate residual moderate to severe neurocognitive impairments. The proportion with poor functional outcome largely depends on the definition of CSWS, comorbidities and causative agents, and the resources that are used to integrate patients in society. However, about half of the published cases demonstrate residual deficits severe enough to make it difficult to live an independent life (Boel and Casara, 1989; Morikawa et al., 1995; Ohtsuka et al., 2002; Roulet et al., 1991; Roulet Perez et al., 1993; Tassinari et al., 1992; Tassinari and Rubboli, 2006). The efficacy of antiepileptic drugs, steroids, or surgical management in modifying long-term neuropsychological outcome remains to be proven.

Predictors of Outcome

Many authors associate frequent spiking and the ESES pattern with cognitive deterioration (Holmes and Lenck-Santini, 2006; Stickgold and Walker, 2007; Tassinari and Rubboli, 2006). Thus, minimizing the EEG abnormalities may potentially have a positive impact on the neurocognitive outcome if this association is correct (De Negri et al., 1995; Iustuska et al., 2006; Scholtes et al., 2005). The duration of ESES seems to be the most important predictor of cognitive outcome (Bureau, 1995a; De Negri, 1997). In a review of 209 cases from the literature, an ESES duration of longer than 2 years was associated with poor cognitive outcome (Rousselle and Revol, 1995), and, in a series of five cases with pre- and postoperative neuropsychological assessment, a tendency toward a better developmental quotient was found in those with later epilepsy onset and a higher proportion of seizure-free lifetime (Loddenkemper et al., 2009b). This contrasts with a series of seven patients in whom there was no association between duration of CSWS and cognitive outcome, although all patients presented a CSWS with minimal duration of 4 years (Scholtes et al., 2005).

Prognostic value of seizure severity or the presence of a structural brain lesion has not been investigated in detail. Interestingly, patients with cortical malformations and CSWS had a better seizure outcome than cases with cortical malformations associated with other epileptic syndromes in one series of 15 patients (Ohtsuka et al., 2002), possibly reflecting the self-limiting course of seizures in CSWS.

TREATMENT

Based on the above outlined outcome parameters, treatment targets seizure frequency, the ESES pattern, and neuropsychological outcome. The treatment choices in CSWS are mostly based on case reports and small case series. It is unclear whether any one anticonvulsant is better than others (Sarco and Takeoka, 2009). Valproate, ethosuximide, and several benzodiazepines may be first-line antiepileptic drugs based on case series (Iustuska et al., 2006; Larrieu et al., 1986; Van Lierde, 1995; Yasuhara et al., 1991). Levetiracetam (Aeby et al., 2005; Wang et al., 2008) or lamotrigine (Guerrini et al.,

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**TABLE 1. Structural Brain Abnormalities Associated With CSWS**

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<th>Van Hirtum-Das et al., 2006</th>
<th>Buzatu et al., 2009</th>
<th>Tas et al., 2009</th>
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<tr>
<td>Patients with abnormal MRI/total patients with CSWS and MRI</td>
<td>33/56 (59%)</td>
<td>18/40 (45%)</td>
<td>44/147 (30%)</td>
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<td>Perinatal vascular etiology/ventricular leukomalacia and related conditions</td>
<td>7/33 (21%) (congenital stroke)</td>
<td>14/18 (78%) (vascular or infectious neonatal injury)</td>
<td>27/44 (61%) (vascular etiology/ventricular leukomalacia)</td>
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<td>Cortical malformation</td>
<td>8/33 (24%) (Cortical dysplasia)</td>
<td>3/18 (17%) (Polymicrogyria)</td>
<td>11/44 (25%) (Malformation of cortical development)</td>
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<td>Abnormal/delayed myelination</td>
<td>5/33 (15%)</td>
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<td>Diffuse atrophy</td>
<td>5/33 (15%)</td>
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<td>Chiari malformation</td>
<td>2/33 (6%)</td>
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<td>Tubers</td>
<td>1/33 (3%)</td>
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<td>Tumor</td>
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Pharmacological Treatment of Seizures and Spiking

The most commonly used drugs for CSWS are valproate, ethosuximide, lamotrigine, levetiracetam, several benzodiazepines, and corticosteroids. Uncontrolled case series of nighttime high-dose oral or rectal diazepam (1 mg/kg up to doses of 30 mg per dose) have been reported to decrease nocturnal spiking by several authors (De Negri et al., 1995; Eksioglu et al., 2009), although frequent relapses prompt new cycles of treatment (De Negri et al., 1995). In a series of 15 patients, high-dose valproate alone or with associated ethosuximide were effective (67%) in the remission of the epileptic syndrome, with a high rate of partial recovery of the mental function, and without relapses after a median of 10 years follow-up (Inutsuka et al., 2006). When valproate in combination with ethosuximide were not effective, two different therapies were tried: (1) short cycles of high-dose diazepam resulted in initial efficacy in two of the four patients, although both patients eventually relapsed; and (2) ACTH was effective in one of the four patients, who relapsed after 6 months (Inutsuka et al., 2006). However, other studies could not reproduce major improvement with similar regimens: valproate and benzodiazepines did not achieve any improvement in seven patients with CSWS and were associated with an adverse behavioral reaction in about half of them (Scholtes et al., 2005); and a case report of CSWS confirmed valproate refractoriness (Okuyaz et al., 2005). Other drugs with therapeutic success in case reports or small case series included lamotrigine (Guerrini et al., 1998; Van Lierde, 1995), clobazam (Larrieu et al., 1986; Van Lierde, 1995), levetiracetam (Aebly et al., 2005; Wang et al., 2008), and clonazepam (Yasuhara et al., 1991). Because of the severity of the seizure disorder, polytherapy is frequently necessary. It is unclear in how far clinical improvement with reduction in the number of drugs in patients on long-term polytherapy (Van Lierde, 1995) reflects the age-related spontaneous improvement of the seizure disorder.

Carbamazepine, phenytoin, and phenobarbital are usually avoided because they are thought to lack efficacy or may worsen CSWS (De Negri, 1997; Guzzetta et al., 2005; Okuyaz et al., 2005; Van Lierde, 1995). Carbamazepine has been associated with generalization of spike and waves (Capizzi et al., 1995; Lerman, 1986). However, improvement after phenytoin (two of four patients) (Inutsuka et al., 2006), as well as lack of worsening with carbamazepine (two patients), or phenobarbital (one patient) has also been reported (Inutsuka et al., 2006).

Immune Modulation Therapy

The use of corticosteroids has led to EEG and clinical improvement in selected cases (Okuyaz et al., 2005; Sinclair and Snyder, 2005; Tassinari et al., 1992). In one series of 44 children with ESES, a prolonged corticosteroid treatment (hydrocortisone 5 mg/kg/day during the first month, 4 mg/kg/day during the second month, 3 mg/kg/day during the third month, 2 mg/kg/day during the following 9 months, and then slowly tapered for a total treatment duration of 21 months) lead to reduction of seizures and/or neuropsychological improvement in 34 of 44 (77%) of cases, achieving complete control of seizures in 34 patients and normalization of the EEG in 21 patients. The long-term remission rate was 45% (Buzatu et al., 2009), but this study may have included less-severe cases [acquired epileptic aphasia (AEA) in 4 cases, opercular syndrome in 2 cases, visual agnosia in 1 case, apraxia/hemis-neglect in 1 case, learning disorder in 3 cases, or frontal syndrome in 18 cases] (Buzatu et al., 2009) possibly contributing to improved outcome. Side-effects associated with corticosteroid therapy generally limit its long-term use.

The efficacy of intravenous immunoglobulin in patients with CSWS has yet to be demonstrated (Arts et al., 2009), but promising results have been reported in a few cases of AEA (Fayad et al., 1997; Lague et al., 1998; Mikati and Saab, 2000; Mikati and Shamseddine, 2005; Mikati et al., 2002).

Surgical Treatment

Epilepsy surgery has been described as a therapeutic modality not only in patients with focal epileptiform discharges but also in patients with generalized EEG patterns and early unilateral brain lesions (Moosa et al., 2010; Wylie et al., 2007). Surgical interventions include multiple subpial transections, focal resective surgery of the epileptic focus, and hemisphreectomy. Multiple subpial transection consists of multiple small superficial parallel cuts in the cortex, severing only the local corticocortical connections in an attempt to disrupt local epileptic circuitry, and has been reported to recover age appropriate speech in seven of a series of 14 patients with AEA (Morrell et al., 1995), whereas a less-dramatic language improvement was found in other series (Cross and Neville, 2009; Irwin et al., 2001). Hemisphreectomy and focal resective epilepsy surgery have been shown to be highly beneficial in controlling seizures and improving the EEG pattern in small series of patients with ESES of structural etiology (Battaglia et al., 2009; Guzzetta et al., 2005; Loddenkemper et al., 2009b). Furthermore, a tendency toward neurocognitive improvement was found in three of five patients after surgery (Loddenkemper et al., 2009b). Data on the long-term neuropsychological outcome of surgically managed patients are not available.

RELATED CONDITIONS AND DIFFERENTIAL DIAGNOSIS

Continuous spike and waves during sleep and related conditions are thought to constitute a clinical spectrum in which benign epilepsy of childhood with centrotemporal spikes (BECTS) and benign occipital epilepsy of childhood (BOEC) represent milder manifestations, while CSWS may be located at the more severe end of the spectrum. Cases with intermediate features in-between entities raise the question of clearly defined borders between these syndromes (Table 2).

BECTS and BOEC

BECTS and BOEC are relatively mild disorders on this spectrum. They are characterized by age-dependent occurrence of focal spikes (centrotemporal or Rolandic in BECTS; predominantly occipital in BOEC). In both syndromes, sleep potentiation has been described. Both can have infrequent focal motor seizures with a semiology that relates to the cortical areas involved (hemifacial twitches, drooling, and anarthria during sleep in BECTS; autonomic seizures in early-onset BOEC; and visual auras in late-onset BOEC) (Panayiotopoulos et al., 2008). Normal neurocognitive function and outcome was classically an integral feature of these syndromes. However, detailed neuropsychological examination may reveal mild cognitive dysfunction in several domains, and—in the setting of
Acquired Epileptic Aphasia Landau–Kleffner Syndrome

Acquired epileptic aphasia presents with progressive language deterioration, usually in 5- to 7-year-old children. Typically, this is an acquired aphasia of subacute onset that worsens over time, although with a fluctuating pattern of spontaneous improvements and exacerbations. Associated behavioral regression is frequently present. The EEG recording shows bilateral centrotemporal, posterior temporal, and parietooccipital interictal spikes, and these become more diffuse during non-REM sleep. The complex relationship between language regression and epileptiform activity in (or near) the primary and associative auditory cortex is discussed elsewhere (Metz-Lutz, 2009; Seri et al., 2009). Despite the severity of the EEG abnormalities, the seizures, if present, are infrequent nocturnal focal motor seizures. They are usually well controlled with most antiepileptic drugs, and spontaneously disappear over time. After a variable period of fluctuating severity, the aphasia tends to stabilize and, usually, improves around the age of puberty (Deonna and Roulet, 1995; Schellens-de Boer, 2009).

The focal discharges of AEA are classically centrotemporal, posterior temporal, and parietooccipital, but it may generalize in sleep resembling an ESES pattern. The ages of onset, its clinical course, and associated neurobehavioral regression of AEA also significantly overlap with CSWS in some patients. Differentiating features include the following:

1. Pattern of regression, most prominently language in AEA, and global regression in CSWS.

2. Seizure severity, usually mild in AEA, but severe with frequent seizures of various types in CSWS.

3. Neuropsychological outcome of AEA.

4. Association with a structural brain lesion, which is rarely seen in AEA (Bhatia et al., 1994; Huppke et al., 2005; Nass et al., 1993; Otero et al., 1989; Perani et al., 1993; Solomon et al., 1993), but occurs in 45% to 59% of cases with CSWS (Buzatu et al., 2009; Tas et al., 2009; Van Hirtum-Das et al., 2006).

Others

Besides these classic entities, a number of intermediate forms, such as atypical benign partial epilepsy (Aicardi and Chevrie, 1982; Doose and Baier, 1989; Verrotti et al., 2002), and acquired epileptiform opercular syndrome (Pascual-Castroviejo et al., 1999; Prats et al., 1992; Shafrir and Prensky, 1995) have been described among other subtypes (Panayiotopoulos et al., 2008). Some authors also consider Lennox–Gastaut syndrome or its variants as a part of this spectrum (Galanopoulo et al., 2000; Yan Liu and Wong, 2000), although it does not present with age-related hyperexcitability and sleep activation is not one of the most prominent features. In Lennox–Gastaut syndrome, the electrical status epilepticus is essentially unrelated to sleep or age (Arzimanoglou et al., 2009; Jayakar and Seshia, 1991).

PATHOPHYSIOLOGY AND MECHANISMS

The mechanisms that lead to the development of the ESES pattern are complex and only partially understood. One possible explanation includes the corticothalamic neuronal network involved in physiological oscillating rhythms between the thalamus and the cortex. This network is thought to be switched to a pathologic discharging mode resulting in the ESES pattern on EEG. Early developmental injury or genetic factors may play a role in this switch. Additionally, the disruption of normal brain development by early developmental lesions, genetic defects, or epileptogenic activity per se may promote the development of pathologically hyperexcitable neuronal networks that further sustain epileptogenic activity.
Neuronal Networks

An anatomically and functionally related group of neurons may constitute a network that can initiate and sustain seizure activity. The activity of any one part of the network would affect the activity of all other parts, because electrical hyperexcitability associated with seizure activity reverberates within the neural structures of the network, independent of the origin. Therefore, the original onset of the electrical discharge may not be as important as the anatomic location of the neuronal network. A disruption at any location within the network may influence the occurrence of seizures or other patterns (Spencer, 2002). Functional imaging studies are delineating the neuronal networks associated with different seizure syndromes, such as absence seizures (Bai et al., 2010; Carney et al., 2010). In CSWS, these studies have found involvement of the perisylvian region, the prefrontal cortex, the cingulate gyrus, as well as the thalamus (Siniatchkin et al., 2010). Therefore, the ESES pattern may be generated in a local network and may become generalized through the corticothalamic circuit.

Thalamic Reverberating Circuit

The thalamic reverberating circuit that gives rise to physiologic oscillations during sleep, such as spindles, may contribute to the generalization of epileptiform discharges in ESES (Kellaway, 1985; Beenakker and Huguenard, 2009). The cyclic interaction between glutamnergic excitatory thalamocortical neurons, in the dorsal thalamic nuclei, and inhibitory GABAergic reticular thalamic (RT) neurons, located in the reticular nucleus, is the basis for the oscillating properties of the thalamus (Beenakker and Huguenard, 2009; Steriade et al., 1993). The RT neurons send inhibitory projections to the thalamocortical neurons, and these neurons send projections to the cortex, and collateral ends back to the RT neurons. An initial inhibition, and subsequent postinhibitory rebound activation is caused by activation of the GABA_B and GABA_A receptors in the thalamocortical neurons. RT neurons delay the activation of thalamocortical neurons, potentially explaining the regular 6 to 14 Hz rhythm of the corticothalamic network and other associated rhythms, such as sleep spindles. The oscillating properties of the circuit are tonically inhibited by the reticular activating system inputs during wakefulness, while the decrease in the reticular activating system activity during non-REM sleep is thought to disinhibit the oscillating properties of the circuit (Beenakker and Huguenard, 2009). These postinhibitory rebound bursting RT neurons also inhibit neighboring RT neurons, thus limiting the number of neurons involved in a particular cycle of network discharge, avoiding an excessive hypersynchrony (Bal et al., 1995; Deleuze and Huguenard, 2006; Sanchez-Vives and McCormick, 1997) (Fig. 2).

Switch From Physiologic to Epileptic Oscillations

The switch from the physiologic oscillation frequency at 6 to 14 Hz to a pathologic slow paroxysmal oscillation frequency of 3 to 4 Hz could be related to the passage from predominantly GABA_A receptor-mediated inhibitory postsynaptic potentials, to predominantly GABA_B receptor-mediated inhibitory postsynaptic potentials (Beenakker and Huguenard, 2009; Kim et al., 1997). GABA_B receptors are associated with a longer latency of synaptic transmission, which could explain the slowing in the frequency (Beenakker and Huguenard, 2009). The loss of GABA_A interneuronal RT inhibition would be responsible for the hypersynchrony of RT neurons and subsequent increase in amplitude of epileptiform discharges. It has been experimentally demonstrated that application of GABA_A receptor antagonists to thalamic tissue transform sparse 6 to 14 Hz spindle-like activity into robust 3 to 4 Hz epileptiform oscillations (Blumenfeld and McCormick, 2000; Huguenard and Prince, 1994; Kim et al., 1997; Sanchez-Vives and McCormick, 1997; von Krosigk et al., 1993). In a similar way, nocturnal activation of melatonin receptors during darkness suppresses hippocampal GABA_A receptor function in rodents, thus resulting in a more excitable temporal lobe during the night (Stewart and Leung, 2005). Chronic treatment with GABA_B receptor antagonists at doses below epileptogenic threshold has also been found to induce a change in neuronal plasticity that promote learning and memory normalization in animal models of Down syndrome (Fernandez et al., 2007). The future development of this therapeutic approach into clinical practice could improve the prognosis of patients with intellectual disabilities (Fernandez and Garner, 2007), although the above cited proconvulsant properties of GABA_A receptor antagonists can complicate their clinical use in epileptic encephalopathies such as CSWS.

Conversely, it has been demonstrated that GABA_B receptor antagonists can eliminate 3 Hz epileptiform activity both in vitro (Kim et al., 1997) and in vivo (Smith and Fisher, 1996). It has also been found that GABA_B receptor antagonism can improve memory in nonepileptic animals (Heln et al., 2005). Furthermore, GABA_B receptor antagonists abolish learning impairment in a rat model of atypical absence, even with low doses that do not influence seizure activity, suggesting that the cognitive impairment is partially independent of the seizure activity and that GABA_B receptor antagonists have a therapeutic potential for the treatment of cognitive impairment in epileptic syndromes (Chan et al., 2006).

Significant GABA_B receptor activation is primarily achieved only with strong presynaptic stimulation (Kim et al., 1997). Therefore, one explanation could be that an insult facilitates strong, synchronized RT neuron bursting, such as a primary epileptic focus in the cortex, and this could cause an imbalance from the normally prevailing GABA_A to a pathologically predominant GABA_B neurotransmission (Beenakker and Huguenard, 2009).

Thalamic lesions may also dysregulate GABAergic neurotransmission in the reticular nucleus and thereby enhance epileptiform discharges (Guzzetta et al., 2005). Several case reports
describe patients with thalamic injury who developed CSWS or sleep potentiating of interictal epileptiform discharges (Incorpora et al., 1999; Monteiro et al., 2001). In a large series, 29 of the 32 patients with early thalamic lesions suffered from ESES or sleep activation of paroxysmal discharges. Lesions were unilateral or predominantly unilateral in most cases, and the reticular nucleus was involved in 91% of cases (Guzzetta et al., 2005). In a large series, 14 of 147 (9.5%) patients with significant sleep-potentiating epileptiform activity had a structural abnormality in the thalamus (Tas et al., 2009).

**Temporary Hyperexcitability**

Because neuronal activity is critical for synaptogenesis and brain development, excitation predominates over inhibition in neuronal networks during the first years of life. As the brain matures, these seizure-predisposing features tend to progressively disappear (Fig. 3).

Glutamate is the main excitatory neurotransmitter in the brain. Inotropic glutamate receptors, such as N-methyl-D-aspartate, and alfa-amino-3-hydroxy-5-methyl-4-isoxazole propionate receptors, are ligand-gated ion channels that permit the flux of ions to a varying degree, depending on their subunit composition (Lau and Zukin, 2007). The immature brain has reduced subunit glutamate receptor-2 expression, which in animal models alters the permeability of alfa-amino-3-hydroxy-5-methyl-4-isoxazole propionate receptors contributing to a lower threshold for seizures (Kumar et al., 2002; Sanchez and Jensen, 2001; Silverstein and Jensen, 2007). Similarly, N-methyl-D-aspartate receptors with high levels of the NR2B, NR2C, NR2D, and NR3A subunits, which are more frequent in the first years of life, promote epileptogenic activity (Rakhade and Jensen, 2009; Silverstein and Jensen, 2007). Third, GABAergic neurotransmission is incompletely developed in the immature rat brain (Swann et al., 1989) and can be excitatory and depolarizing, instead of inhibitory and hyperpolarizing in the immature brain (LoTurco et al., 1995). Regarding the composition of the GABA receptor, the expression of α subunits is low at birth and gradually increases with maturation (Sanchez and Jensen, 2001). The first study on human brain tissue in ESES showed significant differences in receptor subunit composition between samples from epilepsy surgery patients and nonepileptic postmortem controls. Specifically, the glutamate receptor-1/glutamate receptor-2 ratio in alfa-amino-3-hydroxy-5-methyl-4-isoxazole propionate receptors and the NR2B/NR2A ratio in N-methyl-D-aspartate receptors were increased in ESES when compared with controls (Loddenkemper et al., 2009a), findings that mimic the receptor composition of the immature brain, and are compatible with a lowered seizure threshold. Regarding GABA receptors, the α2/α1 ratio was increased in patients with refractory epilepsy, and patients who suffered acute status epilepticus, but did not change in patients with CSWS, potentially suggesting a decrease in GABAAα subunits in patients with CSWS as compared with patients with other types of epilepsy (Loddenkemper et al., 2009a).

**Genetic and Environmental Influences**

The mechanisms that govern brain maturation and seizure susceptibility are mostly unknown. From a genetic point of view, Elongator Protein Complex 4 (ELP4) gene at 11p13 has been implicated in transcription of several genes that regulate the actin cytoskeleton, cell motility, and cell migration of the neurons, specifically during cortical development (Close et al., 2006; Creppe et al., 2009). As several polymorphic markers in the ELP4 gene have been recently linked to the centrotemporal sharp wave EEG trait (Strug et al., 2009), it has been hypothesized that a noncoding mutation in ELP4 gene could impair brain-specific Elongato-mediated interaction of genes implicated in brain development in a way that predisposes to an increased susceptibility to seizures, spikes, and neurodevelopmental disorders (Strug et al., 2009).

Environmental aspects disrupting normal brain development may also play a role. Data from animal research show that the seizing brain suffers a series of changes that modify its function and, in the long-term, structure, making it more susceptible to ongoing seizures that become independent from the mechanism originally causing epileptic activity (Rakhade and Jensen, 2009)—a process referred as kindling. Acute changes include alterations in ion-channel activity, posttranslational changes to proteins, such as neurotransmitter receptors, and immediate gene activation. Subacute changes cause activation of transcription, neuronal death, and inflammation. In the long term, structural changes such as mossy fiber sprouting, network reorganization, and gliosis are seen (Rakhade and Jensen, 2009). Although these mechanisms are thought to be present both in the adult and the child, the secondary disruption of the normal development is seen almost exclusively in the child, in part due to greater plasticity. Normal neuronal activity is known to increase immediate early genes induction and neurotrophic factors secretion, sustaining the structural and functional stability of active synapses (Rakhade and Jensen, 2009). Although this mechanism is up-regulated in the immature brain to potentiate synaptogenesis and the development of physiologic neuronal networks, it is pathologically overactivated in epileptic patients (Rakhade and Jensen, 2009), probably leading to the establishment of pathologic epileptogenic neuronal networks. Early developmental lesions are known to dramatically disrupt the complex interplay between environmental, genetic, molecular, and cellular mechanisms implicated in normal brain development and maturation (Rudolf et al., 2009; Volpe, 2009).

**CONCLUSION AND OUTLOOK**

Continuous spike and waves during sleep and related conditions are likely parts of clinical and pathophysiologic spectrum of temporary hyperexcitability syndromes (Galanopoulou et al., 2000; Smith and Hoepner, 2003; Tassinari et al., 2000, 2009). Etiology is variable, because this syndrome is likely an age-specific response to diverse early neurologic insults. It is unclear whether EEG abnormalities are cause or effect, or merely represent a bystander phenomenon during the development of regression. It is likely that a
third factor, such as an early insult or predisposition leads to temporary network hyperexcitability during maturation presenting with nocturnal spiking and developmental delay. Additionally, there may be an interaction between spiking and genetic or structural insult. Medical and surgical management could be tailored to target the network point with the least likely functional consequences (Spencer, 2002). Given the importance of the thalamus in the suspected underlying network, studies on thalamic modulation with drugs, such as sodium oxybate (Kothare et al., 2007), or thalamic stimulation (Fisher et al., 2010) may eventually provide a novel treatment approach to CSWS.

Although the presence of ESES is a requirement for the diagnosis of CSWS, it is also seen in various stages of other syndromes (De Negri, 1997; Galanopoulos et al., 2000; Rossi et al., 1999; Scholtes et al., 2005). These disorders represent a clinical spectrum with several common features:

1. EEG discharges that increase and generalize during sleep.
2. Neuropsychological deficits or regression.
3. Age-specific presentation, with an onset around 4 to 5 years and a variable stabilization, or even improvement, around the age of puberty.

Disruption of the normal brain development at a critical period due to genetic predisposition or environmental insults, such as an early developmental lesion, may be responsible for a change in neurotransmission that enhances hyperexcitability. The process of kindling can further predispose to continuing seizure activity. Progressive maturation of the function and structure of the brain around puberty could increase the seizure threshold and may explain the age-related resolution of the seizure disorder (Fig 3).

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