Review article

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Encephalopathy with continuous spike-waves during slow-wave sleep: evolution and prognosis

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ABSTRACT – Encephalopathy with continuous spike-waves during slow-wave sleep (CSWS) evolves over time, and three stages can be recognized: before the onset of CSWS, during CSWS, and after the CSWS period. Clinical seizures tend to remit spontaneously around puberty. This pattern is independent of the etiological lesion. The CSWS also disappears in all cases. Focal abnormalities instead, may persist for some time after the disappearance of CSWS. The disappearance of the clinical seizures and CSWS may be simultaneous or seizures may disappear before or after disappearance of the CSWS pattern on the EEG. Electroclinical parameters in the pre-CSWS period that have been proposed to predict a poor outcome are early-onset seizures, appearance of new seizures, and a significant increase in seizure frequency. From the electrical point of view, an increase in the frequency of the interictal EEG paroxysms while awake and during sleep and bilateral spike-and-wave paroxysms may also be predictive of a poor evolution in CSWS. When CSWS disappears, neurocognitive and behavioral status improve, but in most patients, residual moderate to severe neurocognitive impairments remain. In non-lesional epilepsy, cognitive recovery after cessation of the CSWS depends on the severity and duration of the initial regression. The duration of the CSWS seems to be the most important predictor of cognitive outcome. Early recognition and effective therapy to reduce the seizures and resolve the CSWS may be crucial to improve long-term prognosis. Cognitive recovery is observed in patients who respond well to AED treatment and outcome depends on the etiology.

Key words: electrical status epilepticus, evolution, outcome, continuous spike-wave, slow sleep, encephalopathy related to status epilepticus during slow sleep

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Definition and nosological aspects

Encephalopathy with continuous spike-waves during slow-wave sleep (CSWS) is an age-related syndrome characterized by neurocognitive regression, seizures, and an EEG pattern of electrical status epilepticus during sleep. Onset of the CSWS syndrome is typically between the ages of 4 and 7 years with seizures accompanied by developmental regression. The syndrome sometimes presents in children beyond the age of 10-12 years and cases as young as two years of age have been reported (Bureau, 1995; Loddenkemper *et al.*, 2011). CSWS presents in children with structural or metabolic epilepsy associated with different types of brain lesions, it may be related to genetic or probably genetic causes, or the etiology may be unknown. The syndrome may be diagnosed when CSWS occurs in more than 85% of non-REM sleep; however, the classification of the ILAE does not specify a cut-off value (Commission on Classification and Terminology of the International League Against Epilepsy, 1989).

Although the pattern of CSWS is the main diagnostic criterion of the CSWS syndrome, it is also observed in other syndromes that are now considered to be part of the same clinical spectrum, including atypical benign partial epilepsy of childhood (ABPEC), status of benign childhood epilepsy with centrotemporal spikes (SEBCECTS), and Landau-Kleffner syndrome (LKS) (Fejerman *et al.*, 2000; Loddenkemper *et al.*, 2011). All four conditions have been reported as atypical evolutions in children with a previous diagnosis of benign childhood epilepsy with centrotemporal spikes (BCECTS) (Fejerman *et al.*, 2000). Patients with BCECTS may also evolve to a so-called "mixed form of atypical evolutions" showing the CSWS pattern associated with clinical features of ABPEC, SEBCECTS, LKS, and typical CSWS (Fejerman *et al.*, 2000). Additionally, an atypical evolution associated with CSWS has been reported in children with Panayiotopoulos syndrome and in those with childhood epilepsy with occipital paroxysms of Gastaut (Caraballo *et al.*, 2001, 2011).

Landau-Kleffner syndrome shares many clinical and EEG features with the CSWS syndrome; however, in the former it is more often associated with acquired aphasia while in the latter psychiatric disturbances are more commonly found (Tassinari *et al.*, 2000).

CSWS may occur in children with organic brain lesions, of which unilateral polymicrogyria (PMG) is the most common (Caraballo *et al.*, 2013a, 2013b), and shunted hydrocephalus, indicative of thalamo-cortical circuitries (Veggiotti *et al.*, 1998; Caraballo *et al.*, 1999, 2008; Ben-Zeev *et al.*, 2004).

Evolution

CSWS evolves over time, and modifications of clinical seizures, EEG abnormalities, and neurocognition occur. Three stages have been reported (Sánchez Fernández *et al.*, 2012).

In the first stage, before the onset of CSWS, patients often show infrequent nocturnal motor focal seizures: in addition, hemiclonic status epilepticus, absences, atonic, complex focal seizures, and generalized tonic-clonic seizures can often occur. Age at epilepsy onset in the pre-CSWS period peaks between four and five years (range: 2-12 years). In this stage, abnormal EEG findings are observed that always include potentiation of spiking during non-REM sleep. The EEG may show focal or multifocal slow spike-waves predominantly in centro-temporal, frontal, and less frequently, parieto-occipital regions similar to those observed in idiopathic epilepsy of childhood (*figure 1*). Fast spikes, polyspikes, asymmetries, and paroxysmal voltage attenuations, evocative of forms of structural epilepsies, as well as diffuse spike-wave paroxysms at 2.5-3 Hz, may be seen (Caraballo *et al.*, 2013a). After the initial period in which the interictal EEG shows focal abnormalities, the appearance of some particular EEG manifestations, such as an increase of focal abnormalities during sleep and while awake, and bilateral spikes and waves predominantly in the anterior region that increase during sleep may suggest a probable evolution to the CSWS period (*figure 2*).

In the second stage, the seizures become more frequent and complicated with typical or, more frequently, atypical absences, myoclonic absences, absence status epilepticus, atonic or clonic seizures, and generalized tonic-clonic seizures. Tonic seizures do not occur. In this period, the mean age at epilepsy onset is 6.8 years (range: 4-13 years). The interictal activity is much more frequent and severe with more widespread spikes of higher amplitude associated with a more abnormal background. During sleep, the EEG pattern shows CSWS (*figure 3*). The onset of CSWS is accompanied by psychomotor decline with deterioration of IQ, language (expressive aphasia and articulation disorder as well as auditory verbal agnosia), cognitive functions, and behavior (hyperkinesis and bizarre, aggressive, psychotic or autistic behavior, emotional instability) (Seri *et al.*, 2009; Seegmuller *et al.*, 2012). Motor impairment, such as pseudoataxia and even loss of independent gait, worsening of a unilateral deficit, fine motor clumsiness with distorted handwriting, dyspraxia, and dystonia have been described (Fejerman *et al.*, 2000; Seegmuller *et al.*, 2012). In a historical series of 209 published patients with CSWS, Rousselle and Revol (1995) recognized

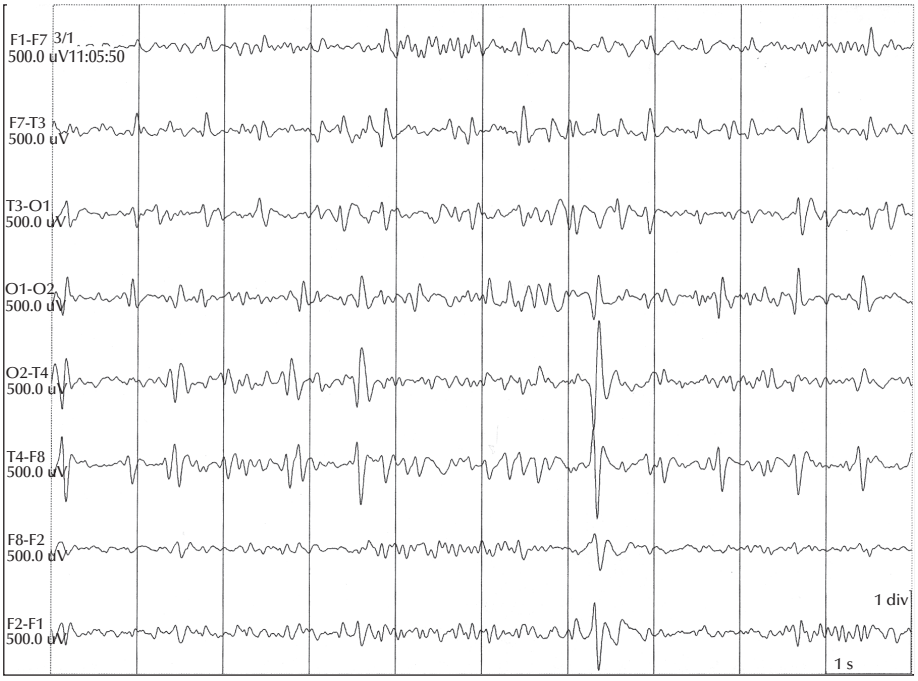

Figure 1. A five-year-old boy who had a focal motor seizure during sleep.
The EEG recording during sleep shows independent bilateral spikes.

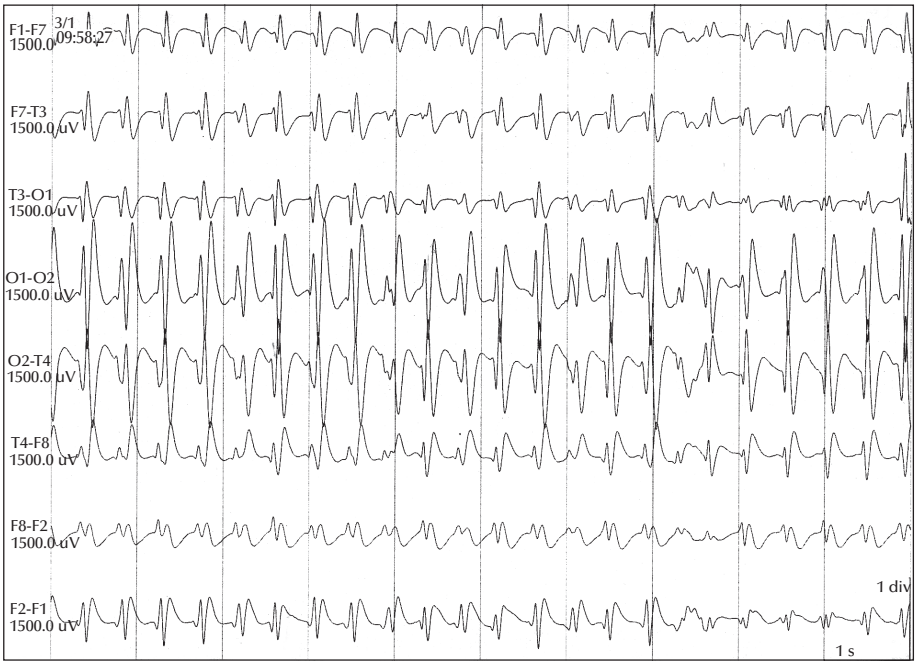

Figure 2. The EEG recording during sleep shows high-frequency spikes in frontal regions.

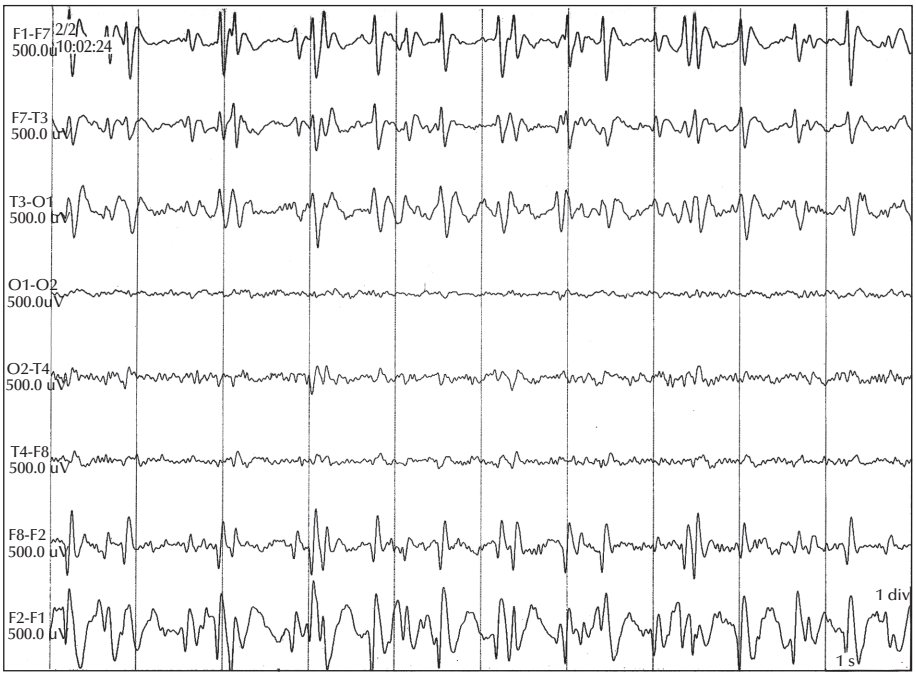

Figure 3. An eight-year-old boy with negative myoclonia, motor deterioraton, and behavioral disturbances associated with right posterior polymicrogyria. The EEG recording during sleep shows continuous spikes and waves during slow sleep predominantly in the right occipital region.

three clinical groups based on neuropsychological profile during the CSWS period. This profile correlated directly with the duration of CSWS and the site of the main epileptogenic focus: Group 1 showed no neuropsychological deterioration. In these children the period of CSWS was of shorter duration and the main epileptiform focus had a Rolandic topography. In Group 2, children had language deterioration (primarily LKS) and the main epileptiform focus found was in the temporal region. In Group 3 (the largest group), children had global neuropsychological deterioration rather than linguistic impairment. The main epileptiform focus was found in the frontal region. Recently, we have reported a series of patients with focal CSWS. Those with focal CSWS in the frontal region showed behavioral disturbances and/or motor deterioration and in those with temporo-occipital involvement language and/or behavioral disturbances were seen (Caraballo *et al*., 2015). In another study, two patients with acquired Kanji dysgraphia who developed CSWS that was dominant in the occipito-temporal region were described showing morphological, phonemic, and semantic errors (Kuki *et al*., 2014). Focal CSWS is an intriguing and challenging entity and this finding underlines the importance of an adequate neurophysiological examination, to localize the functional lesion, as well as a thorough neuropsychological evaluation in individual cases to understand the impact of these particular EEG findings during sleep on brain function (Tassinari *et al*., 2015).

In the third stage (after months to usually two to seven years), the seizures remit and a general improvement can be seen. Whether or not EEG abnormalities persist after the CSWS has disappeared depends on the underlying etiology. Therefore, the interictal sleep and awake EEG should normalize in idiopathic or probably genetic cases. In structural cases, the EEG recordings may show focal, multifocal, or bilateral asymmetric spikes (Caraballo *et al*., 2013a). After the CSWS has disappeared, school performances and IQ may improve significantly in seizure-free patients and in those who have a more than 75% seizure reduction (Caraballo *et al*., 2013a). A recent study has suggested a correlation between neuropsychological outcome and recovery of physiological sleep homeostasis, as measured by impairment of sleep slow-wave activity (SSWA) during ESES and SSWA renormalization after CSWS resolution (Bolsterli *et al*., Epilepsia, 2017; see also Rubboli *et al*., p.S62-S70).

In children with structural or idiopathic focal epilepsies, classic antiepileptic drugs, such as carbamazepine, oxcarbazepine, phenobarbital, or phenytoin, may induce the appearance of CSWS; these should be avoided (Fejerman *et al*., 2000). Similar effects have been reported in sporadic cases with valproic acid, lamotrigine, topiramate, and levetiracetam;

these findings await further confirmation (Fejerman *et al*., 2000). To our knowledge, this phenomenon has not been observed in patients using clobazam, ethosuximide, and sulthiame.

Outcome and prognosis

Seizures almost always disappear with age, even in patients with a static or progressive encephalopathy (Bureau, 1995; Guerrini *et al*., 1998; Tassinari *et al*., 2000; Loddenkemper *et al*., 2011; Caraballo *et al*., 2013a; Sánchez Fernández *et al*., 2013). Thus, this pattern is independent of the etiological lesion, as shown by the age-related remission, also in patients with a malformation of cortical development or a progressive neurodegenerative disease (Loddenkemper *et al*., 2011). Seizure freedom has been reported at around 6-9 years of age, but data are scarce (Sánchez Fernández *et al*., 2013). In any case, clinical seizures tend to remit spontaneously around puberty. The mean duration of epilepsy is 12 years (range: 4-15 years). CSWS also disappears in all cases, with an average persistence until 11 years of age (Tassinari *et al*., 2000). Focal abnormalities instead, may persist for some time after the disappearance of CSWS (Bureau, 1995). The disappearance of the clinical seizures and CSWS may be simultaneous or seizures may disappear before or after disappearance of the CSWS pattern on the EEG (Bureau, 1995).

Electroclinical parameters in the pre-CSWS period that have been proposed to predict a poor outcome are early-onset seizures, appearance of new seizures, a significant increase in seizure frequency, and resistance to a single AED (Dalla Bernardina *et al*., 1989; Kramer *et al*., 2009; Seri *et al*., 2009). From the electrical point of view, an increase in the frequency of the interictal EEG paroxysms while awake and during sleep, bilateral spike-and-wave paroxysms predominantly in anterior regions, and frequent generalized paroxysms may also be predictive of a poor evolution in CSWS (Dalla Bernardina *et al*., 1989).

When CSWS disappears, neurocognitive and behavioral status improve, but residual moderate to severe neurocognitive impairments might persist (see also Arzimanoglou and Cross, p. S71-5). Cognitive deterioration remains unchanged in almost one third of the patients, the majority of whom are structural cases.

In our study of 117 patients with the CSWS syndrome (Caraballo *et al*., 2013a), around 70% of the structural and idiopathic cases regained their previous cognitive level. Similar findings were published in earlier reports (Liukkonen *et al*., 2010).

A study on the long-term outcome after cognitive and behavioral regression in non-lesional epilepsy with CSWS revealed that cognitive recovery after cessation of the CSWS depends on the severity and duration of the initial regression (Saltik *et al*., 2005).

The duration of the CSWS seems to be the most important predictor of cognitive outcome (Bureau, 1995; De Negri, 1997). Early recognition and effective therapy to reduce the seizures and resolve the CSWS may be crucial to improve long-term prognosis (Inutsuka *et al*., 2006). Cognitive recovery is observed in patients that respond well to AED treatment, and further deterioration is halted in the symptomatic/structural and non-idiopathic group. In patients who do not respond to AEDs, however, cognition continues to deteriorate (Caraballo *et al*., 2013a).

In our study (Caraballo *et al*., 2013a), outcome depended on the etiology. The idiopathic group had an excellent prognosis. In the symptomatic/structural and non-idiopathic group, the patients with unilateral polymicrogyria had a relatively good prognosis compared to children with other structural etiologies. Typical EEG findings before and during the CSWS period, such as asymmetric background activity, focal fast spikes, slow waves, polyspikes, and paroxysmal voltage attenuation, were only seen in the symptomatic/structural and non-idiopathic group.

Fejerman *et al*. found that children with an atypical evolution of BCECTS evolving into ABPEC and SEBCECTS had an ultimate good prognosis, while cases evolving into LKS and ECSWS syndrome had a guarded prognosis in terms of language or cognitive and behavioral impairments (Fejerman *et al*., 2000). The outcome of Landau-Kleffner syndrome is variable, however, the prognosis is usually better than that of CSWS (Van Hirtum-Das *et al*., 2006). The seizures generally respond well to antiepileptic drugs and EEG abnormalities disappear after a few years (Caraballo *et al*., 2014). The language disorder, however, may never resolve in almost half of the patients (Soprano *et al*., 1994). As in patients with a structural etiology, the prognosis is often not benign. Early recognition and adequate treatment management may avoid cognitive deterioration and surgical intervention (Caraballo *et al*., 2013b).

Conclusions

The CSWS syndrome is a well-defined disorder associated with focal or apparently generalized seizures, a peculiar EEG pattern, motor impairment, and cognitive deterioration. Both seizures and CSWS disappear over time in the majority of patients. Neuropsychological outcome is often poor. Although CSWS disappears around puberty, epilepsy and cognitive outcome depend on etiology. The age at onset of CSWS and the site of the main epileptogenic focus may influence

long-term neuropsychological outcome and CSWS duration may affect severity of neuropsychological involvement. Cognitive recovery occurs in children who respond to antiepileptic drugs while it continues to deteriorate in those who do not. Further deterioration is halted in the structural group. □

Disclosures.
None of the authors have any conflict of interest to declare.

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