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FULL-LENGTH ORIGINAL RESEARCH

Clinical staging and electroencephalographic evolution of continuous spikes and waves during sleep

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Summary

Purpose: Currently, in continuous spikes and waves during sleep (CSWS) there is a lack of systematic assessments of the clinically relevant stages and the evolution of the electroencephalographic features. The aim of this study is to describe the evolution over time of clinical and electroencephalographic features in CSWS.

Methods: We enrolled patients from our video-electroencephalography (EEG) monitoring unit with CSWS and with overnight EEG studies with at least one overnight assessment per year over a minimum period of 3 years. We studied clinical presentation and electroencephalographic features. We calculated the (1) spike-wave percentage (SWP) as the percentage of 1-s bins containing at least one spike-wave complex and (2) spike frequency (SF) as the number of spikes per 100 s.

Key Findings: Nine children (six boys) met the inclusion criteria during a 15-year period. Seven (78%) had an abnormal development prior to the epilepsy onset, and in two (22%) seizures were the only presenting symptom. Median age at epilepsy onset was 2 years (range 2 days to 4 years), at neuropsychological regression 5.1 years (4–7.7 years), and at seizure freedom 8.6 years (6.5–11.4 years). Median duration and range of clinically relevant stages were as follows: dormant stage (birth-epilepsy onset median 2 years, range 2 days–4 years), prodromal stage (epilepsy onset-neuropsychological regression 3.9 years, range 0.9–7.7 years), acute stage (neuropsychological regression-seizure freedom 2.9 years, range 2.1–6.6 years), and residual stage (after seizure freedom). Seven patients (78%) had a structural lesion on neuroimaging. At last follow-up (median 11.4 years, range 7.2–20.3 years), eight patients (89%) were receiving antiepileptic treatment, and all patients had residual neurocognitive deficits. During the acute stage, SWP was <85% in 13 (42%) of 31 assessments, and after seizure freedom, 3 of 5 patients (60%) had SWP >85%. Evolution of electroencephalographic patterns included increasing-decreasing, continuously elevated, and fluctuating patterns (33.3% each). There was good correlation between SWP and SF (Spearman correlation-coefficient = 0.942; $p < 0.0001$). SF, which can exceed 100%, reflected changes in electroencephalography pattern in more detail than SWP, which cannot exceed 100% and therefore has a ceiling effect.

Significance: Our series systematically studied the age of occurrence of the significant clinical events. These may assist in defining clinical stages, which can provide a useful framework for future clinical trials in patients with CSWS. The severity of the epileptiform discharges on EEG did not always correlate with seizure frequency and severity; epileptiform discharges could be prominent after seizure freedom and fluctuated along the course of the disease. The values of SWP and SF correlated well, but SWP based on 1-s bins has the potential disadvantage of a ceiling effect.

KEY WORDS: Electroencephalogram, Epilepsy, Epileptic encephalopathy, Neurocognitive regression, Seizures.

Continuous spikes and waves during sleep (CSWS) is an epileptic encephalopathy characterized by neurocognitive regression, seizures, and an electroencephalography (EEG) pattern of electrical status epilepticus during sleep (ESES) (Commission on Classification and Terminology of the International League Against Epilepsy 1989; Bureau, 1995a; Tassinari et al., 2000, 2005). ESES is characterized by a marked activation of epileptiform discharges in the

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transition from wakefulness to sleep, leading to a near-continuous, bilateral (or occasionally lateralized) pattern of slow spikes and waves, and this pattern occupies a significant proportion of non–rapid eye movement (NREM) sleep (Commission on Classification and Terminology of the International League Against Epilepsy 1989, Tassinari et al., 2000, 2005).

CSWS and ESES were classically described as following an age-related evolution over time (Fig. S1A) (Bureau, 1995a,b; Tassinari et al., 2000). The evolution of clinical features in patients with CSWS was described in several studies (Bureau, 1995b; Morikawa et al., 1995; Liukkonen et al., 2010), but there has been no systematic assessment of the age of occurrence of relevant clinical events, such as epilepsy onset, neuropsychological regression, and seizure freedom. The course of the EEG features in patients with the ESES pattern has been described in a cross-sectional series, but a description and correlation with the concomitant clinical features is not available (Beaumanoir, 1995). Only seven patients have been followed longitudinally with concurrent description of the evolution of the main clinical and EEG features over time (Morikawa et al., 1995; Praline et al., 2006) (Table S1). A PubMed search with the terms ''CSWS,'' ''ESES,'' and related topics did not reveal previous studies describing longitudinal evolution of clinical features and epileptiform activity in patients with CSWS (Table S1) (Morikawa et al., 1995; Praline et al., 2006; Liukkonen et al., 2010).

Furthermore, when describing the EEG epileptiform activity in CSWS, many authors loosely refer to the percentage of NREM sleep occupied by spikes and waves as spike-wave index, without defining the exact method for calculating it (Tassinari et al., 2000; Saltik et al., 2005; Tassinari et al., 2005; Inutsuka et al., 2006; Loddenkemper et al., 2009; Scheltens-de Boer 2009; Liukkonen et al., 2010).

The present study was designed to address these gaps. Here we aim to (1) systematically assess the timing of occurrence of clinically relevant events and the evolution of the EEG features in CSWS over time and to (2) compare two well-defined measures in the assessment of the EEG epileptiform activity, namely, the spike-wave percentage and the spike frequency. Our data may provide a useful framework for clinical management and future therapeutic trials in CSWS.

Methods

Patients

A patient was considered to have CSWS if the subject had: (1) an age-related seizure disorder, (2) neuropsychological regression in at least two domains of development, and (3) an age-related ESES pattern on EEG (Fig. S1A) (Commission on Classification and Terminology of the International League Against Epilepsy 1989; Bureau, 1995a; Tassinari et al., 2000). We included only patients who had undergone at least three overnight EEG recordings, separated by a minimum of 3 months over a period of at least 3 years between January 1, 1995 and September 1, 2010. EEG recordings were performed based on the best clinical management as decided by the attending epileptologist, and therefore the timing of EEG recordings was independent of clinical stage, that is, all EEGs could have been performed during the same clinical stage. We excluded all patients with (1) tonic seizures, as they are considered to be incompatible with the diagnosis of CSWS (Bureau, 1995a; Tassinari et al., 2000), (2) deterioration limited to a single developmental domain (e.g., acquired epileptic aphasia), or (3) a spike-wave index reported as consistently below 50% in their medical records.

This study was approved by the Institutional Review Board of Children's Hospital Boston.

A complete description of the methods can be found as Supporting Information (Data S1).

Clinical events and evolution

Three clinical events in the evolution of CSWS were specifically assessed: the age at epilepsy onset, the timing of regression, and the age at seizure freedom. All treatments and seizure types were reviewed.

EEG assessment

We assessed the first 5 min of NREM2 sleep during the first NREM sleep cycle in each overnight EEG recording and calculated: (1) the spike-wave percentage as the percentage of 1-s bins with at least one spike-wave complex and (2) the spike frequency as the average number of spike-wave complexes per 100 s.

Neuroimaging

All patients had at least one brain magnetic resonance imaging (MRI) scan. For the purposes of this study, all MRI scans were reviewed by a pediatric neuroradiologist (SPP) blinded to the clinical diagnosis.

Results

Clinical features

Demographic and clinical data

The included and excluded patients in our study are provided in Fig. 1. Nine patients (six males) met all criteria. Seven patients (78%) had an abnormal development prior to the epilepsy onset, and two patients (22%) had seizures as the only presenting symptom. The clinical and demographic features of our patients are summarized in Table 1 and Fig. 2. Additional information on the patients with neonatal seizures can be found as Data S2.

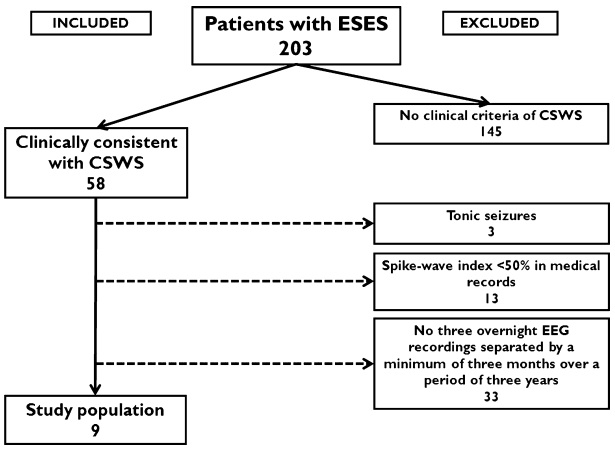

Figure 1.
Included and excluded patients in our study. CSWS, continuous spikes and waves during sleep; ESES, electrical status epilepticus in sleep; EEG, electroencephalography.

Etiologic data

Seven patients (78%) had structural abnormalities on MRI. Three had evidence of an ischemic middle cerebral artery stroke and three of hemorrhagic stroke (grade III intraventricular hemorrhage, bilateral thalamic hemorrhage with intraventricular extension, and a combination of subarachnoid, thalamic, and brainstem hemorrhage with posthemorrhagic hydrocephalus, respectively). One patient had periventricular leukomalacia. The thalamus was affected in five patients (56%). None of the patients had a first- or second-degree relative with epilepsy, but we found a history of epilepsy in a third-degree relative in two patients (22%).

Evolution of the clinical course

The clinical course was described in reference to the typical sequence of three clinically well-defined events in CSWS (epilepsy onset, neuropsychological regression, seizure freedom) and the clinical stages delineated by these clinical events. Epilepsy onset was considered as the time when at least two unprovoked seizures occurred. Because in

Table 1. Clinical and epidemiologic data

P	G/H	Clinical course prior to EO	Age at EO (years)	Etiology/risk factors	Neuroimaging	Age (years) and type of R	Age (years) at SF	Age (years) at last FU	O
1	F/L	R spastic hemiparesis. Cortical blindness	3	Preterm 24 w. Grade III–IV IVH	Atrophy of the left hemisphere. TL	7.4 GM, C, B, S	10.7	20.3	SE
2	M/R	Normal	3.08	IUGR	Periventricular leukomalacia. NTL	4.4 GM, FM, LA, B, S	8.6	11.4	ME
3	M/R	Mild C delay. Spastic quadriparesis with L predominance	0.006	Preterm 30 w. CD. IVH, brainstem, and thalamic hemorrhage	Biparietooccipital and inferior right temporal infarctions. NTL	7.7 C, LA, B, S	NSF	14.3	NI
4	M/L	R hemiparesis. FM delay. Mild delay in LA	0.006	CD. Bilateral thalamic hemorrhage	Bilateral, right greater than left, malacic changes in the thalami. TL	4.8 GM, FM, C, LA, B	11.4	13	SE
5	F/L	Moderate global delay	2	None	Normal. NTL	5.1–6 GM, B	9.8	11.7	SE
6	M/R	Normal	4	CD	Normal. NTL	4.9 GM, FM, LA, B, S	7.5	8.6	SE
7	F/L	R spastic hemiparesis	2.5	PI	Cystic encephalomalacia in left MCA distribution. TL	5.2 C, B	7.3	10	NI
8	M/L	R hemiparesis. R hemineglect	0.67	Unknown. Cocaine use in pregnancy. PI	Encephalomalacia and loss of tissue in left MCA distribution. TL	4 C, B	6.5	8.2	NI
9	M/L	Spastic quadriplegia of R predominance. C delay	0.5	PI	Cystic encephalomalacia in left MCA distribution. TL	6 GM, C, B	NSF	7.2	SE

B, behavioral; C, cognitive; CD, complicated delivery; F, female; FM, fine motor; FU, follow-up; G/H, gender/handedness; GM, gross motor; IUGR, intrauterine growth restriction; IVH, intraventricular hemorrhage; L, left; LA, language; M, male; MCA, middle cerebral artery; ME, mainstream education; NI, not independent/dependent (severely impaired communication/unable to take care of daily needs)/unable to participate in workforce; NSF, no seizure freedom; NTL, no thalamic lesion; O, outcome; PI, prenatal infarct; P, patient number; R, right/regression; S, increase in seizure frequency and/or types; SE, special education/supported employment or enrolled in employment programs for people with disabilities; SF, seizure freedom; EO, epilepsy onset; TL, thalamic lesion; W, weeks.

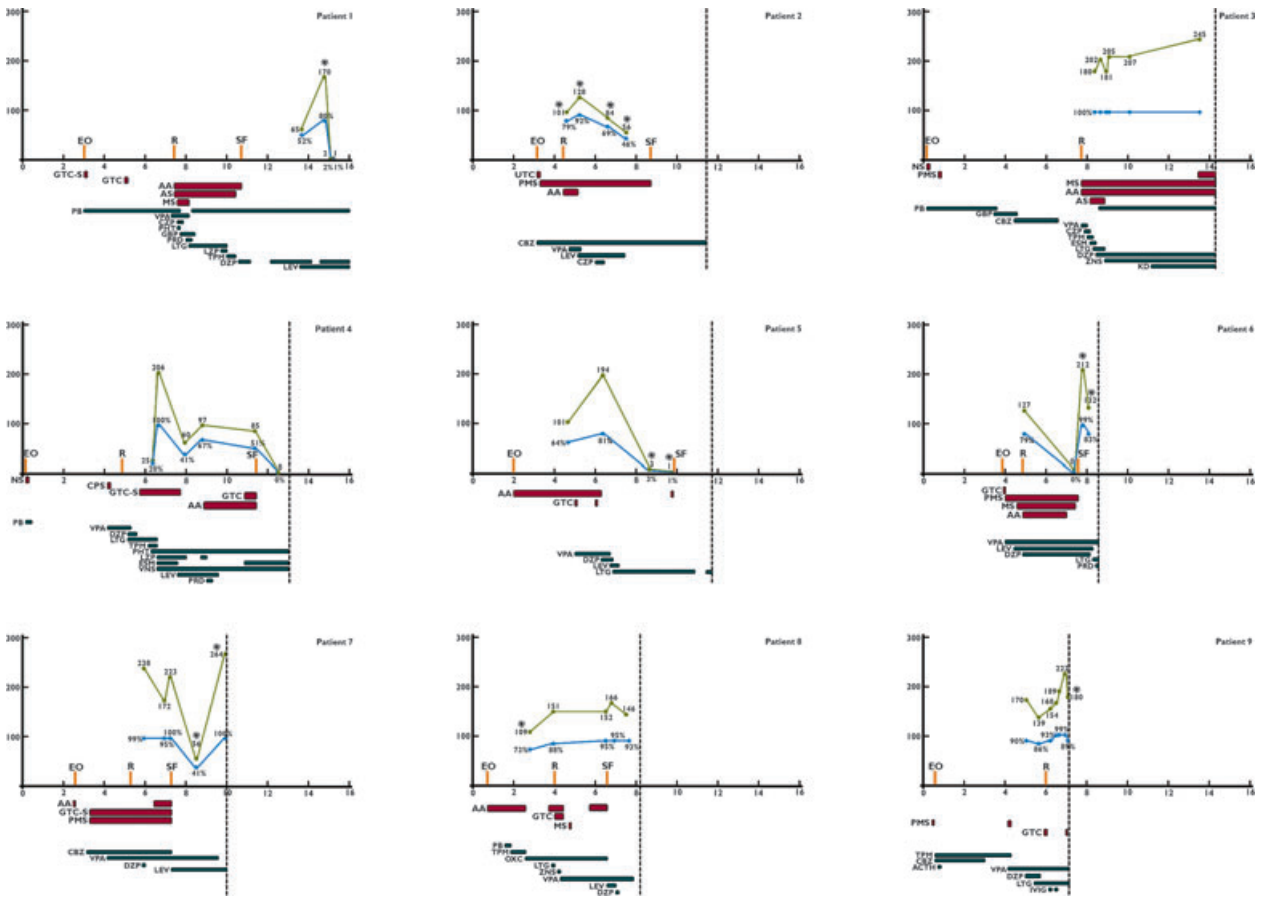

Figure 2.
Graphical representation of clinical and electroencephalographic evolution in nine patients. The x-axis represents age in years. The y-axis represents percentage when referring to spike-wave percentage (blue) or spikes per 100 s when referring to spike frequency (green, specific numbers are plotted above each graph). An asterisk marks an EEG tracing with highly lateralized spike-waves. The vertical dotted line marks the end of follow-up. Antiepileptic treatment regimens are displayed below. The evolution of the EEG epileptiform activity included increasing-decreasing patterns (Patients 2, 4, and 5), continuously elevated patterns (Patients 3, 8, and 9), and erratic patterns (Patients 1, 6, and 7). Four patients had elevated EEG epileptiform activity after seizure freedom (Patients 1, 6, 7, and 8). Note that new seizure types, multiple treatment trials (reflecting the difficult to control epilepsy) and a higher epileptiform activity tend to cluster at a similar age during the beginning of the acute phase. *Clinical events*: EO, epilepsy onset; R, regression; SF, seizure freedom. *Seizure types:* AA, atypical absence; AS, atonic seizures; CPS, complex partial seizures; GTC, generalized tonic–clonic seizures; GTC-S, generalized tonic–clonic seizures with status epilepticus; MS, myoclonic seizures; NS, neonatal seizures; PMS, partial motor seizures; UTC, unilateral tonic–clonic seizures. *Antiepileptic treatments:* CBZ, carbamazepine; CZP, clonazepam; DZP, diazepam; ESM, ethosuximide; GBP, gabapentin; KD, ketogenic diet; LEV, levetiracetam; LTG, lamotrigine; LZP, lorazepam; OXC, oxcarbazepine; PB, phenobarbital; PHT, phenytoin; PRD, prednisone; VPA, valproate; VNS, vagus nerve stimulation; TPM, topiramate; ZNS, zonisamide.

all of our patients the first seizure was unprovoked and was shortly (within 2 weeks) followed by other unprovoked seizures, the age at seizure onset and the age at epilepsy onset coincided in our series. The median age at epilepsy onset was 2 years (range 2 days to 4 years, n = 9), the median age at neuropsychological regression was 5.1 years (range 4–7.7 years, n = 8), and at the last follow-up seven patients were seizure-free for more than a year and had a median age at seizure freedom of 8.6 years (range 6.5–11.4, n = 7) (Fig. S2).

These critical events, if clearly defined in patients, allowed us to divide the clinical course into clinical stages. The duration of the *dormant stage* (birth to epilepsy onset) was 2 years (range 2 days to 4 years, n = 9), the *prodromal stage* (epilepsy onset to regression) lasted 3.9 years (range 0.9–7.7, n = 8), and the duration of the *acute stage* (regression to seizure freedom) was 2.9 years (range 2.1–6.6, n = 6). The prodromal stage plus the acute stage determines the *duration of seizure activity* (i.e., from epilepsy onset to seizure freedom), lasting 5.8 years at last follow-up (range 3.5–11.4,

n = 7). Finally, once seizure freedom is achieved the *residual stage* starts (Fig. S2). Note that the sum of the medians of the duration of prodromal and active stages do not result in the median duration of seizure activity, as not in all patients all clinical stages could be identified.

Treatment

In our series, 8 (88%) of 9 patients were treated with valproate and diazepam, 7 (78%) of 9 patients with levetiracetam, 7 (78%) of 9 patients with lamotrigine, and 2 (22%) of 9 patients with ethosuximide. Immunomodulatory therapy was used in 4 (44%) of 9 patients (prednisone in three and corticotropin [ACTH] and intravenous immunoglobulin in one each). Vagal nerve stimulator and ketogenic diet were used in one patient each. Detailed antiepileptic treatment regimens can be found in Fig. 2. Without a standardized treatment regimen for all patients, comparison of treatment efficacy is not possible (Fig. 2 and Table S2).

Outcome

The median age at the last follow-up was 11.4 years (range 7.2–20.3); eight patients (89%) were still taking antiepileptic medications and all of them had some degree of residual neurocognitive deficits (Table 1).

EEG data

Spike-wave percentage and spike frequency

The evolution of the spike-wave percentage and spike frequency in each patient can be found in Fig. 2 and Table S3.

There was a significant correlation between spike-wave percentage and spike frequency (Spearman correlation coefficient = 0.942; $p < 0.0001$, Fig. S3), but spike frequency reflected changes in the EEG pattern in more detail than spike-wave percentage (coefficient of variation of 56.9% and 47.4%, respectively), especially when the spike frequency was very high (e.g., Patient 3 in Fig. 2). Although spike-wave percentage had a ceiling effect (it cannot exceed 100%), this effect was not seen with the spike frequency.

Evolution of the clinical course and EEG epileptiform activity

The evolution of the EEG pattern included increasing-decreasing (Patients 2, 4, and 5), continuously elevated (patients 3, 8, and 9), and fluctuating patterns (Patients 1, 6, and 7). Four patients had elevated EEG epileptiform activity during the residual stage (Patients 1, 6, 7, and 8) (Fig. 2). The evolution of the overnight EEG tracings during NREM2 sleep in Patient 4 is provided as an example of the changes over time (Fig. 3).

Clinical data showed that: (1) the value of the EEG epileptiform activity, either expressed as spike-wave percentage or spike frequency, can be highly variable during the evolution of CSWS; (2) the spike-wave percentage was <85% in 13 overnight EEG recordings (42%) during the acute stage; (3) although EEG recordings during each stage were not available, the maximum spike-wave percentage and spike frequency were found in the acute or the residual stage; and (4) three patients (of five with EEG data available) in the seizure freedom stage had elevated EEG epileptiform activity with a spike-wave percentage >85% and a spike frequency >140 (Fig. 2).

Discussion

The present case series provides detailed longitudinal data on the clinical and EEG evolution of CSWS. In addition, two different techniques for quantification of EEG epileptiform activity were compared.

Clinical stages

Our data suggest the feasibility of clinical staging in CSWS: *dormant stage* (from birth to epilepsy onset), *prodromal stage* (from epilepsy onset to regression), *acute stage* (from regression to seizure freedom), and *residual stage* (after seizure freedom). The *seizure activity duration* is the duration of *prodromal stage* plus the *acute stage*. There was a tendency toward seizure worsening (more seizure types, more prolonged, more refractory to treatment) shortly after the age of neuropsychological regression (Fig. 2). Patients are refractory to most treatments during the acute phase, but become more responsive near the residual phase. Previous studies on treatment outcome compare CSWS patients at different stages of their disease and are therefore strongly biased because the inherent response to treatment may differ due to spontaneous resolution if patients are enrolled toward the end of the acute phase. The characterization of these stages provides a framework in which the response to treatment in the individual patient may be evaluated in the context of a more or less refractory epilepsy. More importantly, it may allow comparison of treatment outcome in comparable stages of the disease. In addition, it provides important information to patients, families, and health care providers: a highly refractory epilepsy at the beginning of the acute phase may spontaneously improve in around 3 years regardless of available interventions (Figs S1B and S2).

Most series on CSWS apply cross-sectional approaches and pool patients with ESES patterns on EEG data and heterogeneous clinical presentations (Bureau, 1995b; Case Reports, 1995, Saltik et al., 2005; Scholtes et al., 2005; Inutsuka et al., 2006; Buzatu et al., 2009; Liukkonen et al., 2010). All of our patients had regression in at least two developmental domains, epilepsy and an EEG with generalized spike-waves and sleep potentiation consistent with the ESES pattern. These strict inclusion criteria may have led to selection of more severe cases, with a higher frequency of symptomatic epilepsy. This feature could account for the lower age at epilepsy onset in our series (2 years) when

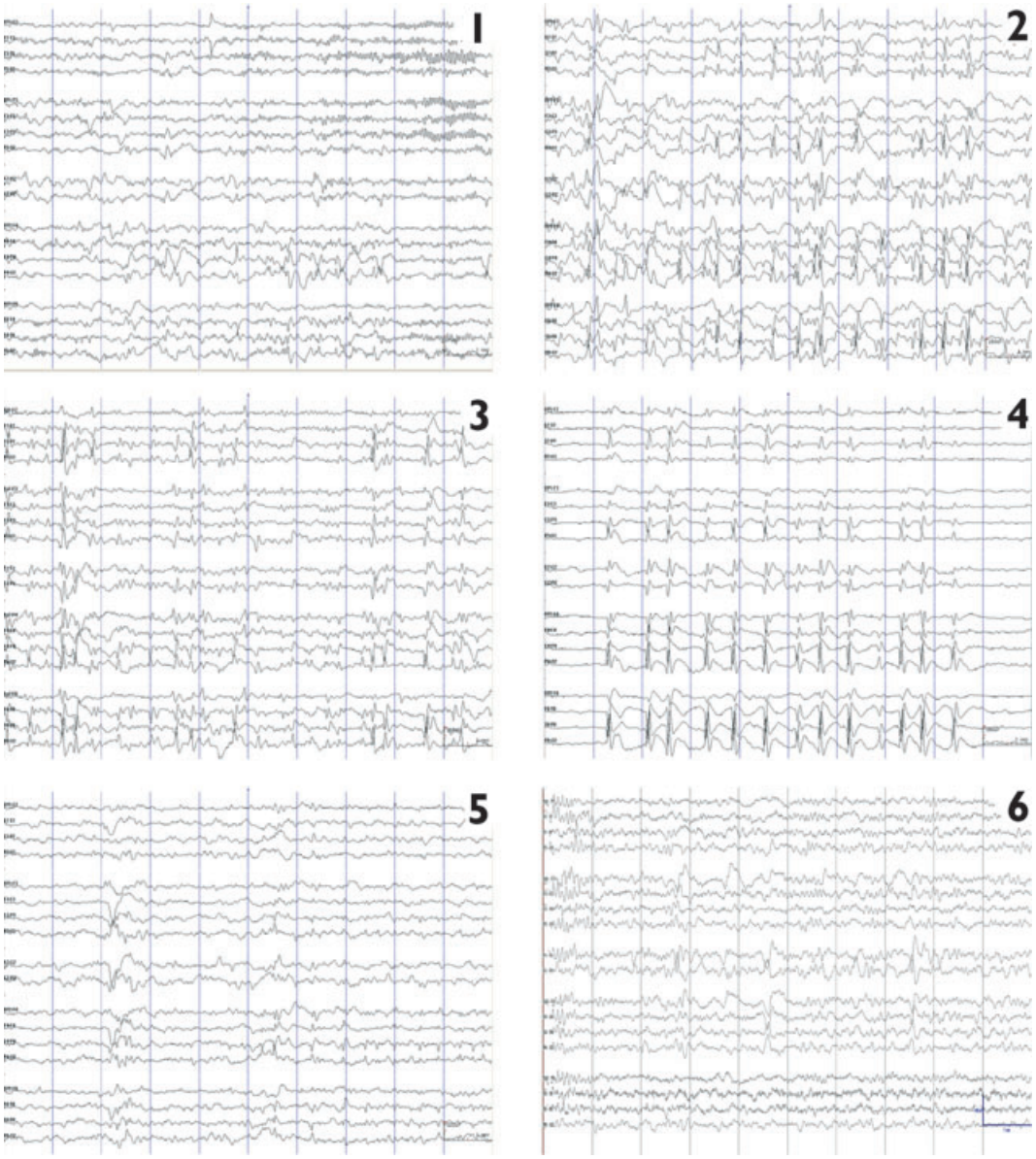

Figure 3.
Evolution over time of the EEG tracing in Patient 4. Every tracing is a sample of stage II sleep in each overnight EEG recording. Note the difference in voltage (the ruler marks 150 mV in 1, 2, 3, 300 μV in 4, 100 μV in 5 and 140 μV in 6). Spike-wave percentage (SWP) and spike frequency (SF) reach a maximum in sample number 2 and subsides progressively: (1) age 6.3 years, SWP 20, SF 25; (2) age 6.6 years, SWP 100, SF 206; (3) age 7.9 years, SWP 41, SF 60; (4) age 8.8 years, SWP 67, SF 97; (5) age 11.3 years, SWP 51, SF 85; (6) age 12.6 years, SWP 0, and SF 0.

compared to classical retrospective series in which epilepsy onset occurred at age 2–5 years (Bureau, 1995a,b; Morikawa et al., 1995; Scholtes et al., 2005). Earlier age of onset in our patient population may be explained by abnormalities on neuroimaging. Another series of children with abnormal neuroimaging and significant sleep-EEG activation had epilepsy onset in the first year of life, similar to our population (Guzzetta et al., 2005). Furthermore, a recent series found that the epilepsy onset was earlier in a symptomatic group than in an idiopathic group (Liukkonen et al., 2010), and a series of 13 patients with symptomatic ESES had an age of epilepsy onset slightly above 2 years (mean 2.3 years, median 2.3 years) (Peltola et al., 2011). Patients with CSWS due to a brain structural lesion may present with an earlier age of epilepsy onset when compared to patients with CSWS without structural lesions.

In our patients, epilepsy onset preceded the first overnight EEG and, therefore, the diagnosis of the ESES pattern by at least 1 year (Fig. 2). This confirms the findings of previous studies in which epilepsy onset occurred around 1–2 years before the diagnosis of ESES patterns (Bureau, 1995a,b; Morikawa et al., 1995; Liukkonen et al., 2010). The timing of regression is addressed in only few reports and tends to be simultaneous with the diagnosis of the ESES pattern, approximately 1–2 years after epilepsy onset (Bureau, 1995a; Morikawa et al., 1995), whereas we found a duration of the *prodromal stage* of 3.9 years. Median age at regression in our series (5.1 years) occurred approximately 1–2 years earlier than in the series of four patients by Morikawa et al. (1995). There has been no reliable data on the timing of regression in the past. Our study offers additional information indicating that regression occurred 2 years after epilepsy onset. These differences may be the consequence of the earlier age at epilepsy onset in our series when compared to classic studies and of the overall scarce previous literature on age at regression. In our series, the median age at seizure freedom was 8.6 years, although it was highly variable, adding to the available literature on age at seizure freedom that reported remission of seizures in an age range of 7–22 years (Morikawa et al., 1995).

Etiologic considerations

There was a higher rate of neuroimaging abnormalities in our series (78%) than in previous literature (30–59%) (Van Hirtum-Das et al., 2006; Buzatu et al., 2009; Tas et al., 2009). Seventy-five percent of our patients had abnormal development prior to the age of regression, which is again higher than the one third of cases described in previous literature (Bureau, 1995a). These differences may again reflect the more strict criteria used to define CSWS in our series compared to the literature, and the subsequent inclusion of patients with severe and symptomatic etiology. The high prevalence of thalamic lesions (56%) in our series is consistent with previous literature (Incorpora et al., 1999; Monteiro et al., 2001; Guzzetta et al., 2005; Tas et al., 2009). Follow-up revealed residual deficits and poor cognitive function in most patients (Table 1).

Evolution of EEG epileptiform activity

In 1995 four patients with CSWS were followed for 13–19 years, and the basic features of their clinical course and the presence or absence of the ESES pattern on EEG were described (Morikawa et al., 1995). In another report, the evolution of the SWI over time was described from age 7–12 years in two siblings with an ESES pattern (Praline et al., 2006). Our series significantly add to the results of these two studies by providing a detailed description of the clinical features over time and attempts to further correlate the clinical and EEG evolution of CSWS.

Spike-wave index cutoff value

The initial definition of CSWS required a generalized spike-wave index of at least 85% (Patry et al., 1971; Tassinari et al., 2000, 2005). Some authors used this percentage (Tassinari et al., 2000; Saltik et al., 2005; Tassinari et al., 2005; Loddenkemper et al., 2009) where others accepted lower percentages as compatible with ESES (Inutsuka et al., 2006; Kobayashi et al., 2006), and the International League Against Epilepsy (ILAE) criteria do not provide a cutoff value (Commission on Classification and Terminology of the International League Against Epilepsy 1989). Our longitudinal data, and the only two cases with a description of the evolution of the spike-wave index (Praline et al., 2006) suggest that there is considerable variability in the EEG epileptiform activity in repeated recordings. Therefore, a spike-wave index of 85% may not be reached every single time during randomly spaced recordings. As suggested by Tassinari's group, the 85% threshold may serve only as ''useful to identify the tip of the iceberg'' (Tassinari et al., 2005). Treatment changes may have contributed to the modification of the quantification of epileptiform activity over time, but patients with CSWS are often treated with several antiepileptic drugs, even before the ESES pattern is recognized and before CSWS is diagnosed. The extent to which treatment changes modify epileptiform activity quantification remains unknown, but static thresholds and cutoff values may not be able to sufficiently mirror the dynamic evolution (secondary to treatment changes or to natural evolution of the disease) of epileptiform activity in patients with CSWS.

Assessment of EEG epileptiform activity

Most authors loosely refer to the percentage of NREM sleep occupied by spike-waves without defining the exact method for calculating it (Tassinari et al., 2000; Saltik et al., 2005; Tassinari et al., 2005; Inutsuka et al., 2006; Caraballo et al., 2008; Kramer et al., 2009; Loddenkemper et al., 2009; Liukkonen et al., 2010; Kevelam et al., 2012). We addressed lack of reproducibility in the counting method by considering the percentage of 1-s bins occupied by at least one spike-wave (Aeby et al., 2005). The selection of bins of 1-s duration makes the counting method straightforward, but it carries the limitation of having a ceiling effect at 100% (i.e., as long as all the 1-s bins are occupied by at least one spike-wave it does not matter whether there are one or four spike-waves per bin: the resulting count will be 100%; Fig. 4). Spike frequency overcomes this limitation by counting the actual number of spike-waves in a given amount of time without predefining bin size. The choice of the denominator (100 s) allows for relatively simple comparison with other denominators.

In addition to heterogenous counting methods, there is no consensus on the selection of specific portions of sleep. Some authors use the overnight NREM sleep tracing (Tassinari et al., 2000, 2005; Inutsuka et al., 2006), others

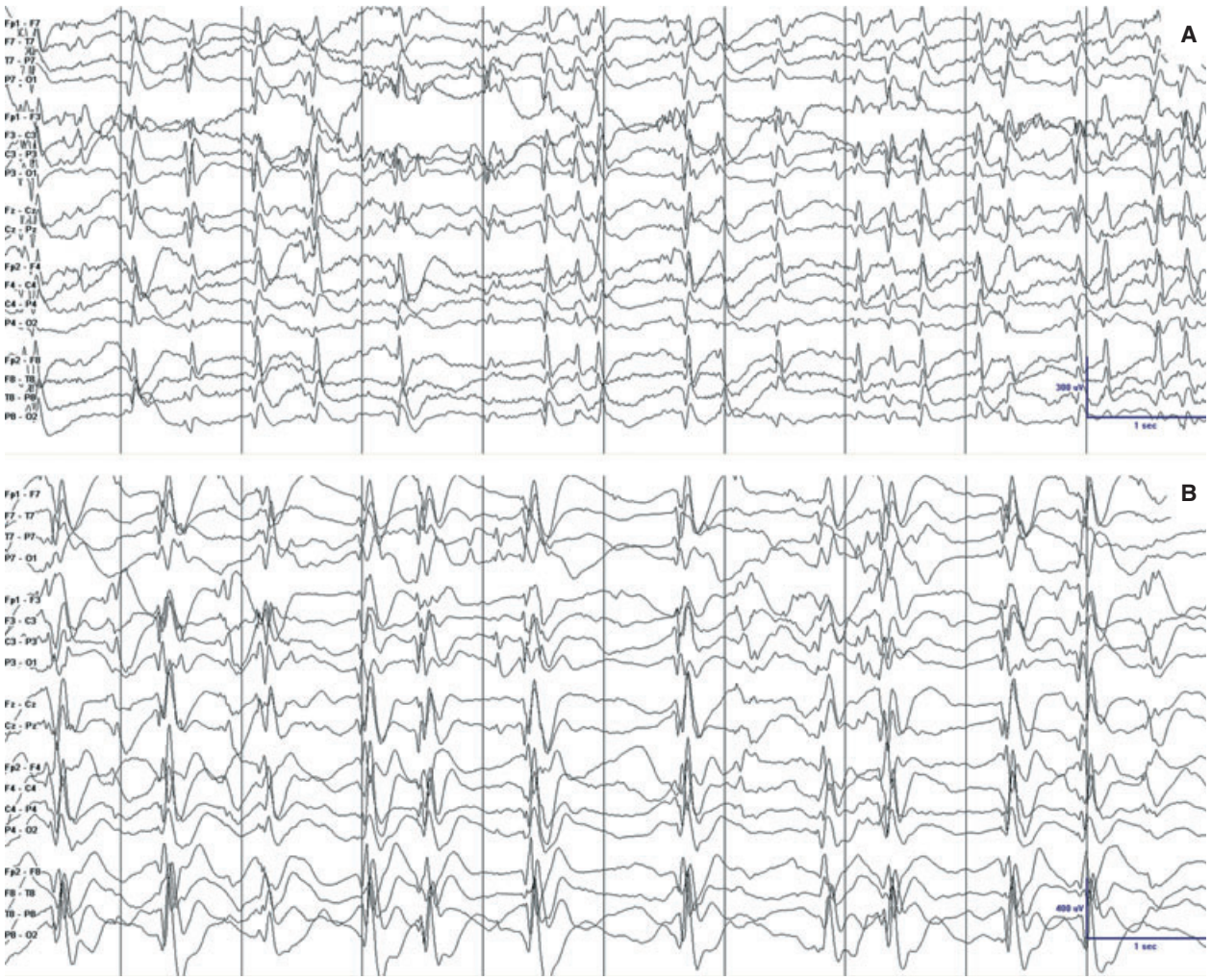

Figure 4.
Different quantification results with different methods of counting in ESES. Epileptiform activity appears much more frequently in (**A**) than in (**B**). Both tracings have a 100% of epileptiform activity, if the reader quantifies the epileptiform activity using spike percentage, that is, counting the percentage of 1-s bins occupied by spike-waves. However, if the reader quantifies the epileptiform activity using spike frequency, that is, the total number of individual spike-waves per unit of time (per 10 s in this page or per 100 s in a longer tracing), epileptiform activity is almost double in (**A**) than in (**B**). Note the different voltages in the different tracings.

use the first 30 min of NREM sleep from the first and last sleep cycles (Aeby et al., 2005), and some select at least one sleep-wake cycle (Saltik et al., 2005), either an overnight NREM sleep, or the first NREM sleep cycle, or nap-EEG (Inutsuka et al., 2006), or simply do not describe which portion of the sleep is used to calculate the percentage (Scholtes et al., 2005; Kelemen et al., 2006; Loddenkemper et al., 2009; Liukkonen et al., 2010). Different timing of EEG assessment with respect to sleep and circadian phases as well as different methods of EEG assessment and quantification may result in considerable variation among available studies. EEG epileptiform activity during the first 5 min of NREM2 sleep is highly correlated with the EEG epileptiform activity measured overnight (Hadjiloizou et al., 2009 [Abstract]) and we provide further data on the validity of sampling the first 5 min of NREM sleep (Data S1). In the future, shorter EEG recordings including sleep may provide reliable spike counts (Larsson et al., 2010) without the need for overnight EEG recordings. Consequently, tracking the evolution of epileptiform activity over time may become easier and less costly. The use of well-defined and replicable methods such as spike-wave percentage and spike frequency would lead to comparable results among different patient series.

Spike-wave percentage and spike frequency

Although spike-wave percentage and spike frequency are highly correlated, it appears that the spike-wave percentage

cannot detect subtle changes due to a ceiling effect (it cannot exceed 100%, Fig. S3) in patients with very active EEG epileptiform activity (e.g., Patient 3 in Fig. 2). The clinical significance of this difference between spike-wave percentage and spike frequency is yet to be determined. Spike frequency provides a more detailed description of the evolution in patients with very active EEG epileptiform activity, and as it does not necessarily depend on the subdivision of the EEG tracing into 1-s bins, so it may lend itself better to an automated, computerized counting than spike-wave percentage or spike-wave index (Chavakula et al., 2009).

Limitations

Data need to be interpreted in the setting of data acquisition. The decision to exclude patients with predominant regression in only one developmental domain (e.g., language in acquired epileptic aphasia) may have led to selection of patients with a more severe condition than in the ESES series in the existing literature. However, firm inclusion criteria are needed to define a homogeneous population of CSWS as in our study. The exclusion of patients with less than three overnight sleep EEG recordings could have also selected a more severe subpopulation of patients and may limit the ability to generalize our findings. However, this is inherent to our study hypothesis because we could not have studied the evolution of the electroclinical features in patients with limited electroclinical data over time. We tried to prevent information bias by recovering and reanalyzing the original EEG tracings.

We have not systematically performed neurocognitive assessments at regular intervals over time. A recent study has prospectively described the evolution of the neurocognitive features in a group of 32 patients with ESES pattern on the EEG and different clinical presentations (Liukkonen et al., 2010). While detailed in the evolution of the neuropsychological features and in the response to treatment, the evolution of the EEG epileptiform activity is not quantified or described over time (Liukkonen et al., 2010). A prospective study that describes the evolution of the ESES pattern with its concurrent clinical course of the seizures and neurocognitive profile would provide much needed insights into the disease process of CSWS. Although there is large variability in the timing and age groups of clinical stages, the description of clinical stages and quantification of EEG activity is a first step toward comparability.

Although we did not imply any pathogenetic mechanism in the definition of the clinical events or in the clinical stages, we found that the age at seizure worsening and the timing of regression were closely related (Fig. 2). The cause of neuropsychological regression in CSWS is incompletely understood and it is possible that epileptiform activity and/or seizures contribute to it or that epileptiform activity, seizures, and neuropsychological regression are distinct manifestations of the same underlying mechanism (Aldenkamp & Arends, 2004; Dodrill, 2004; Majak & Pitkanen, 2004; Holmes & Lenck-Santini, 2006).

When the patient does not have epilepsy, the age at epilepsy onset and the age at resolution of seizures cannot be determined, and the associated stages cannot be defined. In our series we included patients with epilepsy by definition. We recognize, that some patients with ESES and presentations different from CSWS may present with regression only or with regression without seizures (Bureau, 1995b; Tassinari et al., 2000; Loddenkemper et al., 2011). In these patients, we suggest a transition from the dormant stage to the acute stage, without prodromal stage. The residual stage would occur after improvement of neuropsychological features.

EEG recordings were independent of clinical stage, that is, all EEGs could have been performed during the same clinical stage. Although seizures occurred in the setting of the early life insult in two patients, seizures continued in both patients, with later evolution into other seizure types. Early life seizures may occur in the setting of an early life insult, but we feel that it is difficult to separate epilepsy onset immediately after early life insult from an evolving epilepsy presentation later in life based on available clinical features in our patients. Stages, seizures, and EEG biomarkers likely have been affected by the antiepileptic drugs used. However, homogeneous treatment strategies were not feasible because of different treatment approaches of the individual neurologist and the lack of comparability of different disease stages. Ours is the first attempt to overcome this heterogeneity by suggesting clinical events that may serve as comparison points for patients in future trials. Drug regimens with specific protocols in future prospective trials may ameliorate these effects. Placebo-controlled trials are likely not feasible.

Herein we focus on the assessment of the EEG in a standardized way to quantify its epileptiform activity in several clearly delineated clinical stages in CSWS. Future studies will need to address the clinical significance of spike morphology, focality, and other qualitative features not represented by number.

Potential Implications

The occurrence of clinical events and the duration of associated stages may serve as clinical biomarkers in the management and may allow for an estimation of prognosis over time. The quantification of EEG epileptiform activity with objective and reproducible measures may facilitate comparison between different patient series.

Conclusion

We describe clinical events in CSWS that suggest the feasibility of four associated clinical stages. According to our data, the EEG activity does not always correlate with the

seizure activity, can be highly active after seizure freedom, and fluctuates along the course of the disease. Therefore, any static threshold of epileptiform activity on EEG seems arbitrary and insufficient in the diagnostic process of CSWS. The EEG should always be placed in clinical context, and the use of clinical stages and our EEG measures may provide objective diagnostic support during different stages of CSWS. The spike-wave percentage and spike frequency correlate well and should be examined in a larger prospective cohort. Counting of spikes during a defined NREM sleep period, that is, during the first NREM2 sleep cycle, may improve reliability of spike counts in the future. By the same token, avoiding spike counts in the latter part of the night might prevent dilution of the spike-wave index because of the natural propensity of REM sleep to peak in the latter part of the night. The potential advantage of spike frequency over spike-wave percentage (and over the more classical spike-wave index) is the lack of a ceiling effect. The clinical implications of methodologic differences in quantification need further study.

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Disclosures

None of the authors has any conflict of interest to disclose.

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Supporting Information

Additional Supporting Information may be found in the online version of this article:

Data S1. Methods.

Data S2. Case histories of patients with neonatal seizures.

Figure S1. Conventional and proposed models of clinical and electroencephalographic evolution of CSWS.

Figure S2. Clinical stages in our population.

Figure S3. Correlation between spike-wave percentage and spike frequency.

Table S1. Previous studies on the evolution of CSWS and related syndromes.

Table S2. Summary of treatments used in the different stages, and duration of the acute stage.

Table S3. Evolution of the epileptiform activity.

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