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A qualitative awake EEG score for the diagnosis of continuous spike and waves during sleep (CSWS) syndrome in self-limited focal epilepsy (SFE): A case-control study

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ABSTRACT

Purpose: To determine whether awake EEG criteria can differentiate epileptic encephalopathy with continuous spike and waves during sleep (EE-CSWS) at the time of cognitive regression from typical, self-limited focal epilepsy (SFE).
Methods: This retrospective case-control study was based on the analysis of awake EEGs and included 15 patients with EE-CSWS and 15 age-matched and sex-matched patients with typical SFE. The EEGs were anonymised and scored by four independent readers. The following qualitative and quantitative EEG indices were analysed: slow-wave index (SLWI), spike-wave index (SWI), spike-wave frequency (SWF), long spike-wave clusters (CLSW) and EEG score (between grades 0 and 4). Sensitivity and specificity were assessed using receiver operating characteristic (ROC) curves and their reproducibility with a kappa test.
Results: Based on a highly sensitive cut-off, EE-CSWS patients were 8.4 times more likely than those with SFE to have an SLWI > 6%, 15 times more likely to have an SWI > 10 % and six times more likely to have a CLSW of ≥ 1 s. There was substantial agreement between readers (with kappa values of 0.64, 0.69 and 0.67). EE-CSWS patients were 13 times more likely to have an SWF of > 11 % and 149 times more likely to have an EEG score of ≥ 3 than typical SFE patients. Agreement about these ratings was almost perfect (kappa 0.91 and 0.86).
Conclusion: An EEG score of ≥ 3 on a 20-min awake EEG differentiates typical SFE from EE-CSWS at the time of cognitive regression, with good reliability across readers with different levels of expertise.

1. Introduction

Epileptic encephalopathy (EE) with continuous spike and waves during sleep (CSWS) including Landau-Kleffner syndrome (LKS) is a focal epilepsy syndrome of childhood characterised by the combination of regression in cognitive, behavioural and psychiatric functioning and a characteristic electroencephalographic (EEG) pattern, i.e. focal interictal epileptiform discharges (IED) that are activated in NREM sleep stages and tend to spread over the whole scalp [1]. Some cases are related to a specific aetiology (structural cerebral lesion or genetic mutation), but in most cases the aetiology is unknown.

To characterise this EEG pattern better, some authors provide percentages of NREM sleep that must be occupied by the epileptic activity, e.g. > 50 % [2–4] or > 85 % [5], while others combine spike-wave percentages with a qualitative EEG score to characterise the spreading of the spikes and waves [6].

Self-limited focal epilepsy (SFE) is the most common electro-clinical epilepsy syndrome in the paediatric population and represents more than 15 % of all types of epilepsy in children [7]. Among SFE patients, self-limited epilepsy with centro-temporal spikes (ECTS) is the most frequent, with the parieto-occipital type being less common. The diagnosis is based on EEG features, seizure semiology, childhood onset,

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absence of major cognitive deficits and absence of structural epileptogenic lesion revealed by MRI [8].

An overlap exists between non-lesional cases of EE-CSWS and SFE. There are reported cases of evolution from SFE to EE-CSWS, it has been found that SFE and EE-CSWS can coexist within the same family, and both phenotypes are associated with pathogenic variants of the same gene, i.e. GRIN2A [9–11]. This suggests that SFE and EE-CSWS are at the opposite ends of a common spectrum in which the most frequent and diffuse IEDs during NREM sleep result in the more severe behavioural and cognitive deficits [5,12–14].

The diagnosis of EE-CSWS is based on a sleep EEG obtained during a whole night's sleep or a shorter nap. That said, recording a natural sleep EEG in children in the outpatient clinic is not systematically carried out. What's more, it may be particularly challenging in children at the time of behavioural and psychiatric regression and may necessitate an EEG obtained during a drug-induced nap or a whole night's sleep. These investigations are more difficult to organise, more time-consuming and more expensive to carry out than an awake EEG. Although studies on awake EEGs have shown that intermittent slow-wave focus [15], a higher daytime spike frequency [16–18] and spreading of focal discharges to adjacent regions and/or the other hemisphere were more frequent in EE-CSWS compared with typical SFE at the time of cognitive worsening [19], so far no study has specifically looked at whether awake EEG criteria might be able to differentiate EE-CSWS from typical SFE or which awake EEG criteria have the best inter-rater agreement among readers of different levels of expertise.

The goal of this case-control study was to identify qualitative and quantitative indices on awake EEGs that would differentiate EE-CSWS at the time of cognitive worsening from typical SFE with the best inter-rater agreement.

2. Methods

The study was a multi-site retrospective case-control study. Approval to conduct the study was obtained from the Ethics Committee of the Cliniques Universitaires de Bruxelles - Hôpital Erasme (CUB-Erasme, p2018/150, Brussels, Belgium).

2.1. Patient selection

Patients with EE-CSWS, i.e. the case group, were identified from the epileptic database of the CUB-Erasme hospital and the Hôpital Universitaire des Enfants Reine Fabiola (HUDERF) [Queen Fabiola Children's University Hospital]. Patients had to fulfil the following criteria: 1) neurocognitive regression in at least two domains of development (i.e. language, behaviour, learning, memory, attention, social interactions, motor skills and global intelligence, as assessed through comprehensive neuropsychological evaluation; 2) CSWS pattern on a sleep EEG, i.e. focal IED during wakefulness with strong activation and spreading over the whole scalp during NREM sleep; and 3) awake and sleep EEGs carried out at the time of cognitive regression. From this group, we identified CSWS patients sharing the criteria of SFE, i.e. normal pregnancy and childbirth, uneventful past medical history, normal initial psychomotor development up to three years of age, normal neuroimaging, onset between the ages of three and 12, sensorimotor seizures with or without generalisation and/or autonomic or occipital seizures and an EEG showing normal background and focal IED (centrotemporal, mid-temporal, centroparietal, parieto-occipital or occipital) activated upon drowsiness and sleep. The presence of any structural brain lesion revealed by MRI was considered as a criterion for exclusion.

The control group consisted of typical SFE patients. In order to generate an objective evaluation of their everyday cognitive functioning, we chose to evaluate them with the Massa score. This score had already been used in two previous studies assessing EEG criteria that were predictive of the complicated evolution in SFE [15,20]. The cognitive function is classified as "typical" (score of ≤ 2) or "at risk" (score of ≥ 3) according to the sum of academic and behavioural scores. Consequently, the control group fulfilled the following criteria: 1) a Massa score of ≤ 2 indicating that their cognitive function and behaviour were normal [20]; 2) seizures and EEGs including sleep recording consistent with SFE; 3) age and sex that matched those of the case group; and 4) the absence of neurocognitive regression in a follow-up period of at least 48 months [20].

The following clinical data, i.e., sex, Massa score (for SFE patients) [20], neuropsychological profile (for CSWS patients), age of first seizure, EEG localisation of interictal epileptic foci, type of seizure, treatment and IQ (for CSWS patients) were collected from the electronic medical files of each patient.

2.2. EEG analyses

All EEG studies were carried out using 21 scalp electrodes according to the International 10–20 system. Anonymised 20-minute awake and 20-minute NREM sleep EEG segments were created from long-term EEG studies for each patient by author R.S. These two files were randomly and blindly renamed with a number from one to 30 by a medical doctor not participating in the study.

Four quantitative (1–4) and one qualitative (5) EEG indices were selected after an extensive review of the literature on the qualitative and quantitative EEG indices that are useful for characterising the EEGs of EE-CSWS patients: 1) the slow-wave index (SLWI) [20], corresponding to the percentage of focal or diffuse slow activity calculated by dividing the number of seconds demonstrating one or more slow wave complexes in the 20-minute periods divided by 1200 s, multiplied by 100 (SLWI) to express the results as percentages; 2) the spike-wave index (SWI) [4,6], corresponding to the percentage of spike-and-wave (SW) activity in the 20-minute period divided by 1200 s, multiplied by 100 (SWI) to express the results as percentages; 3) the spike-wave frequency (SWF) as the number of SW events in the first 100 s of the EEG [21]; 4) the maximum duration of long spike-wave clusters, i.e. rhythmic SW events during one second or more (CLSW) [20]; and finally 5) a qualitative EEG score that was created by our team in 2005 [6] and which has been used in several publications [22–24], focusing on the background, the presence of slow dysrhythmia, the number of epileptic foci and the presence of secondary generalisation, i.e. high voltage focal spikes registered by more than 80 % of the electrodes. Five grades are defined: grade 0 (normal EEG); grade 1 (normal background, unique focus of SW of low amplitude, Fig. 1A); grade 2 (normal background, multiple ($\geq$2) asynchronous foci of SW of low amplitude, Fig. 1B); grade 3 (normal or unstructured background, intermittent slow-wave focus, high-amplitude SW diffusing to one hemisphere, Fig. 1C or multiple asynchronous foci of SW of high amplitude or unique focus of high amplitude SW with a mirror focus); and grade 4 (unstructured background, intermittent slow-wave focus, high-amplitude SW with secondary generalisation, Fig. 1D).

The anonymised and randomised awake EEG studies were interpreted independently by four physicians: one senior (A.A.) with over 15 years of experience, two intermediate (A.V. and R.S.) with two years of experience and a junior (J.V.) with six months of experience. The anonymised and randomised sleep EEGs were interpreted by author A.A. Only the SWI and the qualitative grading scale were assessed.

2.3. Statistics

All analyses were carried out using the Stata software (Stata version 15 from StataCorp LLC, College Station, Texas, USA). The X^2 test was used for ordinal variables and the two-sample Wilcoxon rank-sum (Mann-Whitney) test was used for continuous variables as they did not follow normal distribution. We considered significant a p-value of $<$ 0.05. Receiver operating characteristic (ROC) curves to determine sensitivity and specificity were carried out with the pooled results of all readers. Then, for each variable analysed, a cut-off was established to dichotomise the results, as close as possible to 95 % for sensitivity, in

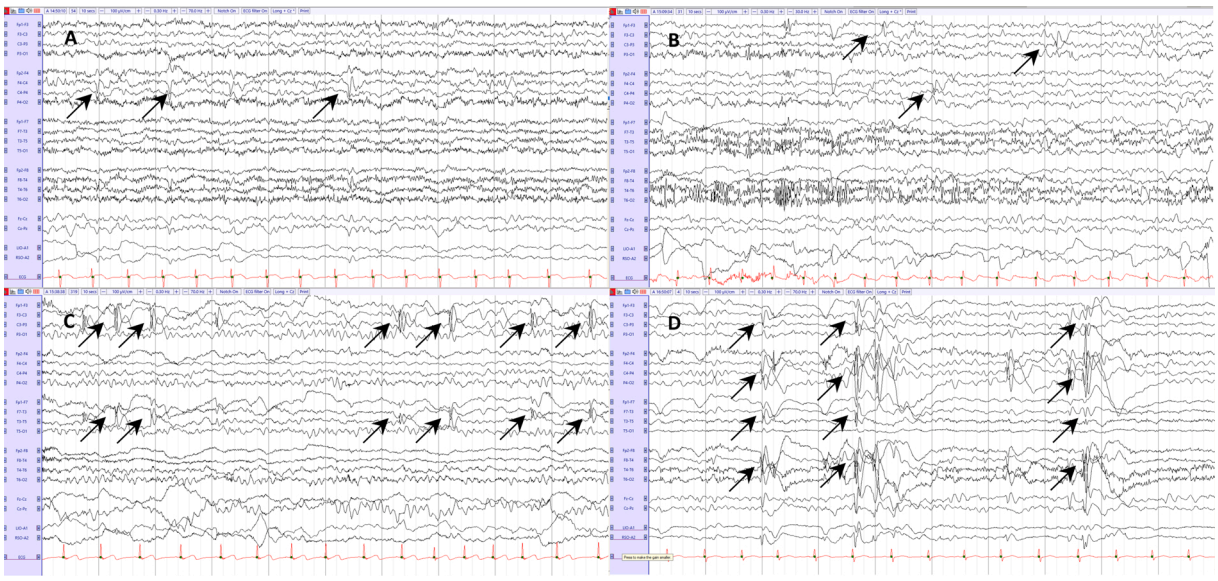

Fig. 1. EEG score used to analyse EEGs (EEG score grade of 0, normal EEG not shown). A) EEG score grade of 1, unique focus (arrow) of spikes of low amplitude; B) EEG score grade of 2, multiple asynchronous foci (arrows) of spikes of low amplitude; C) EEG score grade of 3, intermittent slow wave focus, high-amplitude spike-and-wave diffusing to one hemisphere (arrows); D) EEG score grade of 4, intermittent slow wave focus, high-amplitude SW with secondary generalisation (arrows). The four illustrations are awake EEGs. Time constant: 10 s. Amplitude: 100 μV/cm. High band filter: 0.3 Hz. Low band filter: 70 Hz.

order to minimise false-negative results. A kappa (K) test was also performed to test the inter-rater agreement. K = 0−0.2 indicates slight agreement, 0.21−0.4 fair agreement, 0.41−0.6 moderate agreement, 0.61−0.8 substantial agreement and 0.8–1 almost perfect agreement. [25]

3. Results

3.1. Patients

Among the 45 patients with CSWS identified in the CUB-Erasme (n = 35) and HUDERF (n = 10) epileptic database between 2009 and 2017, 15 patients with EE-CSWS fulfilled the inclusion criteria of SFE. Among the 30 EE-CSWS patients excluded, 23 had a brain lesion and seven had a pre-existing neurodevelopmental disorder. Fifteen typical SFE patients who matched for age at the time of the EEG (respectively 6.2 ± 2.5 for typical SFE and 5.7 ± 2 for EE-CSWS; non-statistically significant, p-value of 0.11) and matched for sex (eight males in both groups) with the case group were then selected as the control group. All patients in the control group had a Massa score of ≤ 2, indicating that they had no cognitive regression with a mean follow-up of 57 ± 4.3 months. All patients in the EE-CSWS group had a cognitive regression, eight with a frontal syndrome, one with LKS, two with hemispatial neglect and apraxia, three with visual agnosia and one with verbal apraxia [11]. Age at first seizure was 5.1 ± 2.0 years in the typical SFE group and 4.1 ± 2.0 years in the EE-CSWS group ($p < 0.02$, statistically significant). Sleep SWI was ≥ 85 % in 15 patients in the EE-CSWS group and in five patients in the typical SFE group. All patients were on an antiseizure medication (ASM) during their EEG in the EE-CSWS group, five on monotherapy and ten on polytherapy, while nine patients in the typical SFE group were on ASM treatment during their EEG, five on monotherapy and four on polytherapy. The detailed electro-clinical characteristics of the control and the case groups are reported in Table 1 (typical SFE) and Table 2 (EE-CSWS) respectively.

3.2. Quantitative and qualitative awake EEG indices

The results are summarised in Table 3. For a defined cut-off value for

Table 1
Electro-clinical characteristics of the typical self-limited focal epilepsy (SFE) group.

Patient no./ sex	Massa score	Age at seizure onset (yr)	Age at the time of EEG (yr)	EEG localisation of interictal foci - type of seizure	Sleep SWI	EEG score	Treatment during EEG
1/M	1	2.5	3	LCP-FM	27 %	A:3-S:3	LEV + VPA
2/M	2	5	6	LCT-FM	93 %	A:4-S:4	NT
3/M	2	3	4	LCT-FGM	94 %	A:1-S:3	LEV + VPA CBZ
4/M	1	4	4	LCT-FGM	10 %	A:1-S:1	NT
5/F	1	2.5	3	RCP-FM	95 %	A:1-S:2	CBZ
6/F	2	3	4	RO-FGM	80 %	A:3-S:4	VPA
7/M	0	4	5	RO-FM	33 %	A:1-S:3	NT
8/F	1	4	5	LC-FGM	91 %	A:3-S:3	LEV + VPA
9/M	0	7	11	CT-FM	19 %	A:1-S:1	NT
10/M	0	9	11	RC-FM	12 %	A:1-S:1	VPA
11/F	0	4	6	RFC-FM	76 %	A:1-S:1	LEV
12/F	1	4	7	RF-FM	66 %	A:1-S:4	NT
13/F	1	8	9	RC-FM	55 %	A:1-S:3	VPA + LTG
14/F	1	7	8	RFC-FM	26 %	A:2-S:2	NT
15/M	2	5	7	LCT-FM	90 %	A:2-S4	VPA

M: male - F: female - A: awake - R: right - CP: centroparietal - S: sleep - L: left - CT: centrotemporal - C: central - F: frontal - CP: centroparietal - O: occipital - F: frontal - FGM: focal and generalised motor - FM: focal motor - VPA: valproic acid - LTG: lamotrigine - CBZ: carbamazepine - LEV: levetiracetam - NT: not treated.

Table 2
Electro-clinical characteristics of the continuous spike and waves during sleep (CSWS) group.

Patient no./age/ sex	Neuropsychological profile	Age at first seizure (yr)	Age at the time of EEG (yr)	IQ or DQ (total or indices)	EEG localisation of interictal foci - type of seizures recorded	Sleep SWI	EEG score	Tt during EEG	Future Tt	Previous Tt
1/F	Frontal syndrome	4	6	70	LCT-AA	95 %	A:4-S:4	VPA	HC	LEV
2/M	Frontal syndrome	5	7	80	LCT-FM	97 %	A:4-S:4	VPA-LTG	HC	LEV-TPM
3/F	LKS	5	6	VCI 64-POI 129	LCT-FM	97 %	A:4-S:4	LEV	HC	VPA-STM
4/F	Right hemispatial neglect and apraxia	2.5	3	71	LCT-AA, NM	95 %	A:3-S:3	VPA-CBZ-STM	HC	ESM-VPA
5/M	Frontal syndrome	3	5	VCI 130-POI 80	RCT-FGM, AA	85 %	A:3-S:4	VPA-TPM	HC	LTG-CLB-LEV-STM
6/F	Visual agnosia	8	9	VCI 110-POI 50	RCP-FM, AA	86 %	A:4-S:4	LEV	HC	VPA
7/M	Verbal apraxia	3	6	VCI: NT-POI 56	LC-FGM	99 %	A:4-S:4	LEV	HC	VPA-CLB
8/M	Frontal syndrome	2	3	NT	RCP-FGM, NM	99 %	A:4-S:4	VPA-STM-CLB	HC	CBZ-LTG-LEV-ESM
9/M	Frontal syndrome	7	9	60	RCP-FGM, AA, NM	96 %	A:4-S:4	VPA-TPM	HC	CBZ-ESM-LEV
10/F	Visual agnosia	2	5	VCI 80-POI 45	LO-FM	87 %	A:4-S:4	VPA	HC	CLB
11/F	Right hemispatial neglect and apraxia	2.5	4	VCI 122-POI 76	LCT-FM, M,AA	100 %	A:4-S:4	VPA-LEV	HC	CLB-ETS
12/F	Frontal syndrome	2.5	4	DQ 70	RCT-FM, M, AA	96 %	A:4-S:4	VPA-LTG	HC-KD-VNS	CLB-TPM-LEV-STM
13/M	Frontal syndrome/4	3.5	5	VCI 52-POI 92	LCT-FGM	97 %	A:4-S:4	VPA-LEV	HC	
14/F	Frontal syndrome/4	4	5	VCI 85-POI 68	LC-FGM, AA	98 %	A:4-S:4	VPA-LEV	HC	CLB-ESM
15/F	Visual agnosia/4	8	9	50	LT-FGM, AA	85 %	A:4-S:4	LTG-ESM	HC	VPA-LEV-CLB

M: male - F: female - LKS: Landau-Kleffner syndrome - A: awake - R: right - CP: centroparietal - S: sleep - L: left - CT: centrotemporal - C: central - O: occipital - T: temporal - G: generalised - AA: atypical absences - FGM: focal and generalised motor - FM: focal motor - NM: negative myoclonia - M: positive myoclonia - Tt: treatment - VPA: valproic acid - CLB: clobazam - HC: hydrocortisone - LTG: lamotrigine - TPM: topiramate - ESM: ethosuximide - CBZ: carbamazepine - LEV: levetiracetam - VNS: vagus nerve stimulation - KD: ketogenic diet - STM: sulthiame - VCI: verbal comprehension index - POI: perceptual organisation index - NT: not testable.

Table 3
Quantitative (SLWI, SWI, SWF, CLSW) and qualitative (EEG score) awake EEG indices analysed to differentiate typical SFE from CSWS and kappa score between the 4 different readers.

Variables	Readers	p-value Mann-Whitney* Chi-square**	AUC ROC	CI AUC (95 %)	Cut-off	LR cut off CI [95 %]	Kappa cut off
SLWI (%)	1 Junior 2 Senior 3 Medium 1 4 Medium 2	0.009* 0.004* 0.08* 0.003*	0.75	0.66 -0.84	>6% Se = 90 % Sp = 48 %	8.4 [2.8–25]	0.64
SWI (%)	1 Junior 2 Senior 3 Medium 1 4 Medium 2	0.003* 0.01* 0.02* 0.01*	0.79	0.71 -0.87	>10 % Se = 93% Sp = 52 %	15 [4–55]	0.69
SWF (%)	1 Junior 2 Senior 3 Medium 1 4 Medium 2	0.01* 0.01* 0.01* 0.01*	0.78	0.70 -0.86	>11 % Se = 93 % Sp = 48 %	13 [3.6–47]	0.9
CLSW (sec)	1 Junior 2 Senior 3 Medium 1 4 Medium 2	0.01* 0.01* 0.02* 0.01*	0.75	0.67 -0.83	≥ 1 s Se = 72 % Sp = 70 %	6 [2.5–14]	0.67
EEG score	1 Junior 2 Senior 3 Medium 1 4 Medium 2	<0.001** <0.001** <0.001** <0.001**	0.92	0.87–0.96	≥3 Se = 98 % Sp = 72 %	149 [7.4–3000]	0.86

SFE: self-limited focal epilepsy - CSWS: continuous spikes and waves during slow-wave sleep - SLWI: slow wave index - SWI: spike-wave index - SWF: spike wave frequency - ClSW: cluster of spike-wave - AUC: area under the curve - ROC: receiver operating characteristic - CI: confidence interval - LR: likelihood ratio - Se: sensitivity - Sp: specificity.

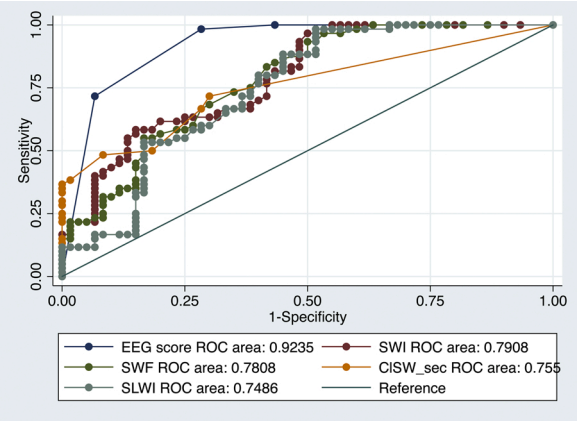

Fig. 2. Area under the curve (AUC) for the EEG score (blue), the SWF (green), the SLWI (grey), the SWI (red) and the CLSW (orange). (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article).

sensitivity set at 95 %, patients with EE-CSWS were 8.4 times more likely to have an SLWI > 6%, 15 times more likely to have an SWI > 10 %, 13 times more likely to have an SWF > 11 %, six times more likely to have a CLSW ≥ 1 s and 149 times more likely to have a grade of ≥ 3 on the EEG score compared with control patients. ROC curves are shown in Fig. 2.

3.3. Interobserver agreement among four independent readers

From a defined cut-off established to have a sensitivity nearest to 95 %, a kappa (K) test was performed for the qualitative and quantitative indices. An SLWI of > 6% (K = 0.64), an SWI of > 10 % (K = 0.69) and a CLSW of ≥ 1 s (K = 0.67) were associated with substantial agreement, while an SWF of > 11 % (K = 0.9) and a grade of ≥ 3 on the EEG score (K = 0.86) were associated with almost perfect agreement.

4. Discussion

This study shows that five easy-to-perform quantitative or qualitative awake EEG indices can differentiate EE-CSWS at the time of cognitive regression from age-matched typical SFE patients, and that the qualitative EEG score is definitively the most accurate index: EE-CSWS patients were 149 times more likely to have a grade of ≥ 3 on the EEG score than typical SFE with an almost perfect inter-rater agreement between physicians with different paediatric EEG reading expertise. This is a critical finding in clinical practice.

Most previously published studies on awake EEG analyses have focused on ECTS with the objectives to compare patients with and without cognitive impairment (15, 16, 18) or to predict which patients will evolve to EE-CSWS in performing longitudinal EEG studies (19, 20). In a retrospective study comparing six ECTS patients with educational impairments to 20 ECTS patients with a typical academic level, Nicolai et al. found that the presence of intermittent slow-wave focus during wakefulness was associated with educational impairments [15]. In a prospective study on 20 ECTS patients, Fonseca et al. found that ECTS patients with a low score on a reading school performance test had significantly more SW events per minute compared with ECTS patients with superior or mean scores (11.7 vs 5; $p < 0.01$) [18]. In a prospective study, Weglage et al. compared IQ in three groups of 12 patients each: patients with frequent or very frequent spikes, patients with no spikes or a single spike, and controls. Patients with very frequent spikes scored significantly lower on Full-scale IQ and performance IQ than patients with no spikes or a single spike and healthy controls ($p < 0.05$) [16]. In our study, even if patients had a more severe cognitive deficit (i.e. cognitive regression versus cognitive impairment), we were similarly able to find that patients with EE-CSWS were more likely to have an SLWI > 6%, an SWI > 10 % and an SWF > 11 % than typical SFE without cognitive impairment. We were also able to demonstrate that SFE patients with long clusters of SW (i.e. repetitive SW ≥ 1 s) were six times more likely to have EE-CSWS, which is an original finding. This is in line with a prospective study on 35 ECTS patients at the beginning of their epilepsy, showing that the presence of clusters of SW of more than six seconds was associated with the evolution to EE-CSWS in 10 of them, nine to 39 months later [20]. In a follow-up study of 16 patients with ECTS who later evolved to EE-CSWS, spreading of focal discharges to adjacent regions and/or the other hemisphere during an awake EEG was present in 64 % of EE-CSWS patients [19]. Similarly, we found in this study that patients with EE-CSWS were more likely to have a grade of ≥ 3 on the EEG score during an awake EEG, illustrating that spreading of focal spikes to other parts of the brain during wakefulness might be an important factor in the pathophysiology of cognitive regression in epilepsies with CSWS. This hypothesis is supported by functional imaging studies with positron emission tomography (PET) using (^{18}F) fluorodeoxyglucose (FDG) and EEG-fMRIs carried out in patients with CSWS that showed altered regional glucose metabolism at rest and altered spike-related brain perfusion at the focus of spikes but also in distant connected areas [22,26–29]. Because these functional neuroimaging studies were carried out when patients were awake, the impact of the spreading of focal spikes not only during sleep but also during wakefulness on cognition should be explored more specifically in future studies.

Interestingly, in this regard we found that the classical SWI ≥ 85 % during sleep was not always associated with EE-CSWS. Indeed, five of 15 patients in the typical SFE group (see Table 1, 2 and 3) had an SWI of > 85 % during NREM sleep without any cognitive and behavioural impairment, as assessed by a Massa score of ≤ 2 during a mean follow-up of 57 ± 4.3 months. We suggest that cognitive regression in CSWS might best be explained by the spreading and/or generalisation of high-amplitude SW events during sleep and wakefulness than by the intensity of spiking. This hypothesis is supported by three previously published studies carried out in our group that assessed the efficacy of drugs in CSWS. In the study on the effect of steroids on CSWS, all but two of the 37 patients who showed cognitive improvement had an improved EEG score (a decrease of at least two grades not only during sleep EEGs but also during awake EEGs) [24]. In the study that assessed the efficacy of levetiracetam in CSWS, we showed that, among the nine patients who clinically improved after two months of treatment, seven had an improvement in their EEG score but only three with a significant reduction of SWI [6]. Finally, in a PET-FDG study carried out among nine children during acute and recovery phases of CSWS, two of them had a regression of metabolic abnormalities at recovery with a substantial regression of the EEG score but still with very frequent IEDs during wakefulness and NREM sleep [23]. This suggests that the EEG score on the qualitative index might be better correlated than the classical qualitative sleep SWI on cognitive functioning in CSWS patients [6]. The quantitative indices, i.e. the SWI, SLWI, SWF and CLSW indices, are based on the counting of the spikes or slow waves during a defined period (100 s, five minutes or 20 min for SLWI, SWI, 20 min for CLSW and 100 s for SWF) [4,20,21]. This procedure requires maintaining one's attention on a repetitive activity for an extended period of time, which increases the risk of error. On the contrary, the EEG score at the qualitative index is fast, easy to perform and extremely reliable. All these observations suggest that the qualitative EEG score might be more suitable than the quantitative indices to analyse an EEG when a patient is suspected of having CSWS-related cognitive regression.

Like any retrospective study, our study carries a risk of methodological bias. Nine of the patients in the control group (60 %) and all our patients in the EE-CSWS group were on an ASM (but none on steroids) at the time of their long-term EEG recordings, which might disturb the distribution of epileptiform activity during wakefulness and sleep. As the founder of the EEG score, we should argue that the high level of

reproducibility of this index could be explained by its extensive use in our clinical practice. Nevertheless, although our team members use the other four EEG indices in their practice extensively, their Kappa score was not as good as the EEG score, except for the SWF, which was not developed by our group. Nevertheless, assessing its reproducibility in sleep by external readers not familiar with the EEG score would be of great interest in confirming its high inter-rater agreement. Although this study is the second largest in the number of patients, it remains a small study in view of the rarity of EE-CSWS. Therefore, the results of this study should be confirmed by a future study involving more patients. We limited our study to non-lesional EE-CSWS patients. Consequently, concerns should be raised about the generalisability of the awake EEG score in the diagnosis of EE-CSWS in patients with structural abnormalities. Finally, a new study that prospectively compares the yield of awake and sleep EEGs in the diagnosis of EE-CSWS should be considered, as a sleep EEG remains the gold standard to diagnose this epilepsy syndrome.

5. Conclusion

This study shows that a grade of ≥ 3 on a qualitative EEG score on an awake EEG could diagnose which patients with SFE are at risk of presenting with EE-CSWS cognitive regression, with an almost perfect agreement across readers from different levels of paediatric EEG reading expertise. Moreover, it suggests that the EEG score on a qualitative aspect should be preferred to quantitative indices to analyse an awake EEG when a patient is suspected of having CSWS-related cognitive regression.

Declaration of Competing Interest

The authors report no declarations of interest.

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We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

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