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Letter to the Editor

The EEG score is diagnostic of continuous spike and waves during sleep (CSWS) syndrome

Epileptic encephalopathy (EE) with continuous spike and waves during sleep (CSWS) is a focal epilepsy syndrome of childhood characterised by the combination of regression in cognitive functioning and a characteristic electroencephalographic (EEG) pattern that may complicate self-limited focal epilepsies (SFE) and focal epilepsies secondary to a structural brain lesion (Van Bogaert, 2013). Although several indices have been developed to calculate the intensity of epileptic activity, there is no consensus to determine what is the best index nor from which cut-off EE-CSWS can be differentiated from uncomplicated focal epilepsy. In a previous retrospective case-control study based on the analysis of different awake EEG indices including 15 patients with EE-CSWS and 15 age- and sex-matched patients with typical SFE, we demonstrated that the qualitative EEG score on an awake EEG differentiated EE-CSWS at the time of cognitive worsening from typical SFE (Aeby et al. 2021). The goal of the current study is to identify, in the same population of the aforementioned study, which quantitative or qualitative indices in non-rapid eye movement (NREM) sleep can differentiate EE-CSWS from typical SFE.

A detailed description of the study design and patients' characteristics can be found in Aeby et al. (2021). Anonymised and randomised 5-minute NREM sleep EEG segments were characterised based on two quantitative and one qualitative EEG indices: (1) the spike-wave index (SWI) corresponding to the percentage of spike-and-wave (SW) activity, calculated by dividing the number of seconds demonstrating one or more SW by the length of the extract, multiplied by 100 to express the results as percentages; (2) the spike-wave frequency (SWF) corresponding to the number of SW events in the first 100 s of the EEG; and finally (3) the qualitative EEG score with five grades: grade 0 (normal EEG); grade 1 (normal background, unique focus of SW of low amplitude); grade 2 (normal background, multiple ($\geq$2) asynchronous foci of SW of low amplitude); grade 3 (normal or unstructured background, intermittent SW focus, high-amplitude SW diffusing to one hemisphere, 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 SW focus, high-amplitude SW that spread to >80% of the electrodes) (Aeby et al., 2021). The sleep EEG studies were interpreted independently by four physicians (A.A., senior; A.V. and R.S., medium and J.V., junior) for the 3 EEG indices and by an automated algorithm (Nonclercq et al., 2012) for the SWI and the SWF. All analyses were made with the Stata software (version 15, Stata Corp LLC, College Station, Texas, USA). The Chi-square test was used for ordinal variables and the two-sample Wilcoxon rank-sum (Mann-Whitney) test for continuous variables. We considered a p-value <0.05 significant. Receiver operating characteristic (ROC) curves to determine sensitivity and specificity were carried out with the pooled results of all readers. Then, for each variable, a cut-off was established to dichotomise the results, as close as possible to 95% for sensitivity. A Kappa coefficient was calculated to test the inter-rater agreement.

The results are summarised in Table 1. The SWI and SWF cut-off values for sensitivity set at 95% were respectively 72% and 108. For these cut-off values, patients with EE-CSWS were respectively 36 times and 31.5 times more likely than patients with typical SFE to cross that threshold. Substantial agreement was found among readers (K = 0.79 and 0.71, respectively). A previous study showed that the intensity of epileptic activity in NREM sleep was associated with cognitive impairments in SFE (Nicolai et al., 2007), but these results could not be confirmed in several prospective and retrospective studies (Cantalupo et al., 2019). Nevertheless, experts have considered variable cut-offs for the quantitative threshold in the diagnosis of EE-CSWS, ranging from >85% to >25% for the SWI and >100 for the SWF (Cantalupo et al., 2019). Even if our results agree with the expert opinion, the low reproducibility of these thresholds in the literature might suggest that quantifying the intensity of epileptic activity with the SWI or the SWF in NREM sleep might not be the best way to diagnose EE-CSWS, as indicated by several experts in the field (Cantalupo et al., 2019).

Interestingly, patients with EE-CSWS were 79.3 times more likely to have an EEG score = 4 in NREM sleep compared with typical SFE, with an almost perfect agreement (K = 0.90). In our awake EEG study, we showed that EE-CSWS patients were 149 times more likely to have a grade of $\geq$3 on the EEG score (Aeby et al., 2021) than typical SFE. Because the EEG score is a qualitative score that characterises the spreading of focal SW our results suggest that spreading of focal SW to other parts of the brain plays a crucial role in the pathophysiology of cognitive regression in EE-CSWS. This hypothesis is supported by functional imaging studies that showed altered regional metabolism at rest and altered spike-related brain perfusion at the focus of SW but also in distant connected areas like the default mode network (Van Bogaert, 2013). The quantitative indices, i.e. the SWI and SWF are based on the counting of the spikes during a defined period. 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. This suggests that the EEG score reflecting the spreading of the focal SW, might be more suitable than the classical SWI or SWF, reflecting the intensity of spiking, both in the sleep and in the

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Table 1
Quantitative (SWI, SWF) and qualitative (EEG score) sleep EEG indices analysed to differentiate typical SFE from CSWS and kappa score between the different readers.

Variables	Readers	Value of EEG indices for SFE patients (median; IQR)	Value of EEG indices for CSWS patients (median; IQR)	p-Value Mann-Whitney* Chi-square **	AUC ROC	AUC 95% CI	Cut-off	OR [95% CI] at that cut-off	Kappa at that cut-off
SWI	1 Junior 2 Senior 3 Medium 1 4 Medium 2 5 Automated algorithm	66; 61 66; 65 60; 50 66; 49 73; 46	92; 16 97; 4 85; 12 94; 14 96; 10	0.001* 0.0001* 0.001* 0.0002* 0.001*	0.86	0.80–0.92	≥72% Se = 95% Sp = 60%	36 [7.6–171.4]	0.71
SWF	1 Junior 2 Senior 3 Medium 1 4 Medium 2 5 Automated algorithm	66; 83 67; 119 100; 70 85; 82 110; 108	153; 65 186; 73 150; 85 164; 65 214; 94	0.0007* 0.0007* 0.003* 0.001* 0.0002*	0.84	0.78–0.91	≥108 Se = 96% Sp = 57%	31.5 [6.9–144.6]	0.79
EEG score	1 Junior 2 Senior 3 Medium 1 4 Medium 2	3; 2 3; 3 3; 2 3; 2	4; 0 4; 0 4; 0 4; 0	0.0002** 0.0007** <0.0001** 0.0001**	0.91	0.86–0.96	=4 Se = 93% Sp = 85%	79.3 [10.6–592.2]	0.90

Legend: EEG: electroencephalogram – SFE: self-limited focal epilepsy – CSWS: continuous spikes and waves during slow-wave sleep – SWI: spike-wave index – SWF: spike-wave frequency-IQR: interquartile range – AUC: area under the curve – ROC: receiver operating characteristic – CI: confidence interval – OR: odds ratio – Se: sensitivity – Sp: specificity.

awake EEG to analyse an EEG when a patient is suspected of having EE-CSWS (Aeby et al., 2021).

Author contributions

AA, and AVH performed the follow-up of the patients, designed the study, characterised the EEG indices and wrote the manuscript. RSL and JV characterised the EEG indices. ANE performed the statistical analysis. XDT contributed to data interpretation and revised the manuscript. PVB performed the clinical follow-up of the patients and review the manuscript. ANO performed the automated analysis of the EEG indices and review the manuscript. Project carried out with the support of the Fund iris-Recherche, managed by the King Baudouin Foundation.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

References

Aeby A, Santalucia R, Van Hecke A, Nebbioso A, Vermeiren J, Deconinck N, et al. 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. Seizure 2021;84:34–9.

Cantalupo G, Pavlidis E, Beniczky S, Avanzini P, Gardella E, Larsson PG. Quantitative EEG analysis in Encephalopathy related to Status Epilepticus during slow Sleep. Epileptic Disord 2019;21:S31–40.

Nicolai J, van der Linden I, Arends JB, van Mil SG, Weber JW, Vles JS, et al. EEG characteristics related to educational impairments in children with benign childhood epilepsy with centrotemporal spikes. Epilepsia 2007;48:2093–100.

Nonclercq A, Foulon M, Verheulpen D, De Cock C, Buzatu M, Mathys P, et al. Cluster-based spike detection algorithm adapts to interpatient and intrapatient variation in spike morphology. J Neurosci Methods 2012;210(2):259–65.

Van Bogaert P. Epileptic encephalopathy with continuous spike-waves during slow-wave sleep including Landau-Kleffner syndrome. Handb Clin Neurol 2013;111:635–40.

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