Research article

Diagnostic utility of specific abnormal EEG patterns in children for determining epilepsy phenotype and presence of structural brain abnormalities

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HIGHLIGHTS

- Centrotemporal spikes have 70% specificity to diagnose childhood epilepsy with centrotemporal spikes (CECTS)/atypical CECTS.
- Photoparoxysmal response has a high specificity for genetic generalized epilepsy of 92%.
- Asymmetric sleep spindles are a better indicator of structural brain abnormality than asymmetric physiologic photic driving.

ARTICLE INFO

ABSTRACT

Objective: Estimate sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) of EEG findings: centrotemporal spikes, photoparoxysmal response, asymmetric photic driving, and asymmetric sleep spindles, for epilepsy phenotype and presence of structural brain abnormalities.
Methods: In this case-control study we reviewed children referred for EEG over a 4-year period, with at least one of centrotemporal spikes, photoparoxysmal response, asymmetric photic driving, or asymmetric sleep spindles. This cohort was analyzed in combination with a research database of pediatric patients with seizures.
Results: Centrotemporal spikes had 100% sensitivity for childhood epilepsy with centrotemporal spikes or atypical childhood epilepsy with centrotemporal spikes, but lower specificity (70%) and PPV (58%). Photoparoxysmal response had high specificity (92%) and NPV (92%) for genetic generalized epilepsy. Asymmetric photic driving had low sensitivity for structural brain abnormalities (17%), with specificity 80%. In contrast, asymmetric sleep spindles had much higher sensitivity and specificity, 44% and 97%, respectively.
Conclusions: Although centrotemporal spikes are classically associated with childhood epilepsy with centrotemporal spikes, these discharges are seen in other conditions. Photoparoxysmal response is highly indicative of a genetic generalized epilepsy, though may be seen in other epilepsy phenotypes. Relative attenuation of sleep spindles is a more reliable indicator of structural brain malformation than asymmetric photic driving.
Significance: The quantitative diagnostic utility of EEG findings should be considered when incorporating these results into clinical decision-making.

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1. Introduction

Scalp electroencephalography (EEG), a technique developed over 90 years ago, is commonly used to evaluate cerebral function and assess an individual's risk for seizures [1]. Over time, the typical physiologic patterns have been well-characterized, as well as common abnormal patterns. Some examples of commonly observed EEG abnormalities include centrotemporal spikes, photoparoxysmal response, asymmetric photic driving response, and asymmetric sleep spindles.

Centrotemporal spikes are medium to high amplitude focal epileptiform discharges that occur over the central or temporal regions, and often have a characteristic horizontal dipole; these discharges are classically associated with childhood epilepsy with centrotemporal spikes, and analysis can help assess risk for seizure recurrence [2, 3, 4, 5]. Centrotemporal spikes may be seen in other forms of epilepsy; however, the precise percentages are not known [6, 7, 8, 9]. Centrotemporal spikes have been found in up to 5% of individuals with no history of seizures, though the abnormality is much more common in close relatives of patients with focal epilepsy [10, 11, 12]. Photoparoxysmal response refers to spikes or spike and wave discharges in response to intermittent photic stimulation [13]. Photoparoxysmal response does not necessarily signify epilepsy as it is a common EEG finding with average incidence of 7.6% in healthy children [13]. However, photoparoxysmal response has clinical relevance as photic stimulation is the most frequent form of trigger for generalized seizures such as absences, generalized tonic-clonic convulsions or myoclonic jerks [14].

The photic driving response is defined as EEG waves that occur at the same frequency of intermittent photic stimulation [15]. While photic driving is physiologic, asymmetric photic driving may suggest cerebral dysfunction on the side of the attenuated response, though the finding has also been noted in children with autism spectrum disorder [16]. Sleep spindles are another physiologic phenomenon, defined as spindle-like rhythmic activity between 11 and 16 Hz, usually having duration less than 2 s, and occurring during sleep [17]. Unilateral attenuation of sleep spindles may be a sign of dysfunction of the ipsilateral hemisphere.

Although these EEG patterns are seen frequently by neurophysiologists, and have generally universal definitions, the precise clinical significance of each is not well-understood, particularly since EEG analysis was revolutionized by the advent of digitization [18]. The sensitivity and specificity of each finding as indicators of cerebral dysfunction is unknown, as are the range of abnormalities that may be associated. In this study we endeavoured to determine the diagnostic value of these findings for children having EEGs at a tertiary pediatric hospital.

2. Methods

This retrospective observational case-control study reviewed all children who had EEG studies at the Montreal Children's Hospital over a 4-year period from April 2016 to April 2020. Montreal Children's Hospital is a tertiary pediatric centre; approximately 10 000 EEG studies were performed during the period of this study. The most common reasons for EEG tests to be ordered at our centre are: (1) events of possible seizure, (2) known epilepsy to assess for subclinical seizures or a change in interictal activity, (3) clinical regression to rule out continuous spike-wave in sleep, (4) encephalopathy. A minority of our EEG studies are ordered by community physicians; in these cases, patients with abnormal EEGs are almost always referred to neurology, so reliable clinical data is usually available.

A 4-year review period was chosen based on power calculation tables published for sensitivity and specificity by Bujang and Adnan [19]. Using centrotemporal spikes as an example, for a predicted prevalence of 5% in our study population and considering a difference in sensitivity of 30% clinically significant, using power of 0.80 and p-value of 0.05, the minimum number of affected subjects and total subjects would be 20 and 400, respectively.

The inclusion criteria were an EEG study including at least one of centrotemporal spikes, photoparoxysmal response, asymmetric photic driving, or asymmetric sleep spindles, and age <18 years at the time of the EEG. We included routine, sleep-deprived, and prolonged video EEG studies, as well as home ambulatory recordings. Studies were primarily identified from a clinical logbook that tracks specific abnormalities such as these. The definitions for the EEG abnormalities were as follows:

(1) Centrotemporal spikes: Medium or high amplitude focal spikes or spike-wave discharges with maximum negativity over the central or temporal regions, and maximum positivity over the frontal regions. The discharges could be unilateral or bilateral.
(2) Photoparoxysmal response: During photic stimulation, occipital or generalized spike-wave discharges are seen.
(3) Asymmetric photic driving: Photic driving is seen but amplitude over one hemisphere is <50% of the other hemisphere, for at least one stimulation frequency.
(4) Asymmetric sleep spindles: Sleep spindle amplitude over one hemisphere is consistently <50% of the other hemisphere.

All EEG studies reported to include one of these findings were reviewed by MA, a pediatric neurology resident, and EM, a clinical neurophysiology scientist and Master of Science in Medicine (Clinical Neurophysiology), to confirm inclusion criteria were met. For any questionable cases, EEGs were reviewed by KAM, a pediatric epileptologist and neurophysiologist, who made the final determination as to whether the study should be included. If a child had more than one EEG during the review period they were classified per the most abnormal of the EEGs (e.g., if a child had an EEG with unilateral centrotemporal spikes and then a subsequent EEG with bilateral centrotemporal spikes, they would be classified as having bilateral centrotemporal spikes). The group of children who had EEG studies meeting the pre-defined inclusion criteria were compared with a group of children with similar demographics enrolled in the Neurodevelopmental Disorders Database/ Biobank, who had an EEG study at the same laboratory during the same period that did not include of any of the findings of interest. The Neurodevelopmental Disorders Database/Biobank is a local research database comprised primarily of patients recruited from the Pediatric Epilepsy Clinic at the Montreal Children's Hospital – all patients presenting with seizures are recruited.

For all included patients, the medical chart was reviewed, and the following data extracted: epilepsy syndrome/phenotype, seizure frequency, developmental history, and neuroimaging results. For any patients for whom there was disagreement on the syndromic diagnosis, we used the International League Against Epilepsy (ILAE) website, epilepsydiagnosis.org, as a reference, and the final decision was made by a qualified epileptologist. The 2022 ILAE epilepsy syndrome classification and definitions were not used as they were not yet available at the time the study was conducted [20, 21, 22].

In statistical analysis, we calculated sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV), along with 95% confidence intervals for each. IBM SPSS Data Software was used for all calculations. For centrotemporal spikes, these calculations were made for a diagnosis of childhood epilepsy with centrotemporal spikes or atypical childhood epilepsy with centrotemporal spikes. For photoparoxysmal response, calculations were made for a diagnosis of juvenile myoclonic epilepsy and for a diagnosis of genetic generalized epilepsy. For asymmetric photic driving and asymmetric sleep spindles, calculations were made for presence of a focal structural brain abnormality identified on neuroimaging, including only patients who had available MRI results.

This study was approved by the McGill University Health Centre Research Ethics Board (MUHC REB; 2021-6619). The Neurodevelopmental Disorders Database/Biobank is also approved by the MUHC REB (2018-3937); written informed consent has been obtained from all patients in that study or their caregivers.

Table 1. Demographic data.

EEG Finding	Centrotemporal spikes	Photoparoxysmal response	Asymmetric photic driving	Asymmetric sleep spindles	Overall	Controls
Number	103	34	24	30	191	98
Age in years (mean ± SD)	8.0 ± 2.8	11 ± 4.2	8.0 ± 4.0	4.6 ± 4.5	7.9 ± 4.0	7.4 ± 4.3
Sex (M/F)	59/44	12/22	12/12	22/8	105/86	62/36
Diagnosed with Epilepsy (%)	95 (92)	29 (85)	12 (50)	23 (77)	155 (81)	88 (90)

EEG = electroencephalography, SD = standard deviation.

Table 2. Specific epilepsy diagnoses in children with centrotemporal spikes.

Epilepsy Diagnosis	CECTS	Focal Structural Epilepsy	Focal Epilepsy Unclassified	Other Epilepsy Syndromes
N (95)	60 (64%)	23 (24%)	4 (4%)	8 (8%)
Age in years (mean ± SD)	8.6 ± 2.7	6.5 ± 3.0	8.5 ± 4.0	7.8 ± 2.3
Sex (M/F)	37/23	10/13	2/2	6/2
Unilateral centrotemporal spikes (N = 47)	24 (51%)	16 (34%)	2 (4%)	5 (11%)
Bilateral centrotemporal spikes (N = 48)	36 (75%)	7 (15%)	2 (4%)	3 (6%)

CECTS = childhood epilepsy with centrotemporal spikes, SD = standard deviation.

Table 3. Diagnostic value of centrotemporal spikes for childhood epilepsy with centrotemporal spikes.

Patient Group	Sensitivity (95% CI)	Specificity (95% CI)	PPV (95% CI)	NPV (95% CI)
All children with centrotemporal spikes	1 (0.94–1)	0.70 (0.61–0.77)	0.58 (0.52–0.64)	1 (N/A)
Children with normal development and neurological examination and centrotemporal spikes	1 (0.94+-1)	0.83 (0.75–0.89)	0.75 (0.66–0.81)	1 (N/A)
Children with normal development and neurological examination and *unilateral* centrotemporal spikes	1 (0.86–1)	0.88 (0.80–0.93)	0.63 (0.51–0.74)	1 (N/A)
Children with normal development and neurological examination and *bilateral* centrotemporal spikes	1 (0.90–1)	0.94 (0.88–0.98)	0.86 (0.73–0.93)	1 (N/A)

CI = confidence interval, N/A = not applicable, NPV = negative predictive value, PPV = positive predictive value.

3. Results

A total of 191 children (105 males, 86 females) were included in the study aged 2 months to 17 y (mean ± SD: 7.9 ± 4.0), including 103 with centrotemporal spikes, 34 with photoparoxysmal response, 24 with asymmetric photic driving, and 30 with asymmetric sleep spindles. Details of the demographics of the subgroups are in Table 1. The control group included 98 children (62 males, 36 females) with mean age 7.4 y (SD 4.3 y); 20 of these children had normal EEG and 88 had a diagnosis of epilepsy. Detailed results with associated confidence intervals are in Tables 2, 3, 4, and 5.

3.1. Group A: children with centrotemporal spikes

This group included 103 children (59 boys and 44 girls). The children's ages ranged from 2 to 16 years (mean ± SD: 8.0 ± 2.8). Fifty-one children (50%) had unilateral centrotemporal spikes and 52 (50%) bilateral centrotemporal spikes on the EEG studies. Ninety-five (92%) of the children with centrotemporal spikes were diagnosed with epilepsy, while the remaining eight did not meet criteria for epilepsy either because they had had only one seizure not typical for childhood epilepsy with centrotemporal spikes, or the EEG was done for other reasons (e.g. developmental regression). Of those with epilepsy, 60 (64%) were diagnosed with childhood epilepsy with centrotemporal spikes or atypical childhood epilepsy with centrotemporal spikes and 23 (24%) had focal structural epilepsy (Table 2). The remainder had either unclassified focal epilepsy or other epilepsy syndromes (Panayiotopoulos syndrome, Gastaut syndrome, childhood absence epilepsy. In children with epilepsy and unilateral centrotemporal spikes, 51% had childhood epilepsy with centrotemporal spikes or atypical childhood epilepsy with

centrotemporal spikes and 34% had focal structural epilepsy. For children with epilepsy and bilateral centrotemporal spikes, 75% had childhood epilepsy with centrotemporal spikes or atypical childhood epilepsy with centrotemporal spikes and 15% had focal structural epilepsy. Among the 95 children with centrotemporal spikes and epilepsy, 80 had normal neurological exam and developmental history at baseline; 60 of these (75%) were diagnosed with childhood epilepsy with centrotemporal spikes or atypical childhood epilepsy with centrotemporal spikes.

Among the children with abnormal brain MRI, only 9 had normal development and neurological exam at baseline. Eight of these had unilateral centrotemporal spikes and only one bilateral centrotemporal spikes on EEG. The other 18 children with abnormal brain MRI had either a history of abnormal development or an abnormal neurological exam. For the 73 children with centrotemporal spikes and normal development and neurological examination, 65 (88%) had normal brain MRI. The sensitivity, specificity, PPV and NPV of centrotemporal spikes for childhood epilepsy with centrotemporal spikes or atypical childhood epilepsy with centrotemporal spikes are in Table 3.

3.2. Group B: children with photoparoxysmal response

We identified 34 children with photoparoxysmal response (13 boys and 21 girls) with ages ranging from 2 to 17 y (mean ± SD: 11 y ± 4.2 y). Twenty-nine (85%) had diagnoses of epilepsy, including 26 (76%) with genetic generalized epilepsy. Among children with genetic generalized epilepsy, 12 had juvenile myoclonic epilepsy, 5 childhood absence epilepsy, 4 epilepsy with eyelid myoclonias (Jeavons syndrome), 2 juvenile absence epilepsy, and 3 genetic generalized epilepsy not better classified.

Table 4. Diagnostic value of photoparoxysmal response for juvenile myoclonic epilepsy and genetic generalized epilepsy.

Patient Group	Sensitivity (95% CI)	Specificity (95% CI)	PPV (95% CI)	NPV (95% CI)
Genetic generalized epilepsy	0.76 (0.59–0.89)	0.92 (0.85–0.96)	0.76 (0.62–0.87)	0.92 (0.86–0.95)
Juvenile myoclonic epilepsy	0.92 (0.64–1.0)	0.82 (0.73–0.88)	0.35 (0.27–0.45)	0.99 (0.94–1.0)

CI = confidence interval, NPV = negative predictive value, PPV = positive predictive value.

Table 5. Diagnostic value of asymmetric photic driving and asymmetric sleep spindles for focal structural brain abnormalities.

Patient Group	Sensitivity (95% CI)	Specificity (95% CI)	PPV (95% CI)	NPV (95% CI)
Asymmetric photic driving	0.17 (0.07–0.31)	0.80 (0.68–0.90)	0.39 (0.21–0.60)	0.56 (0.52–0.61)
Asymmetric sleep spindles	0.44 (0.32–0.58)	0.98 (0.88–1.0)	0.97 (0.80–1.0)	0.56 (0.51–0.62)

CI = confidence interval, NPV = negative predictive value, PPV = positive predictive value.

Five children had no history of seizures, and 3 had focal epilepsy. Of the 5 children without seizures, 4 had a family history of epilepsy.

In the control group, there were 8 children with genetic generalized epilepsy: 3 with childhood absence epilepsy, 1 juvenile myoclonic epilepsy, 1 juvenile absence epilepsy, and 3 with genetic generalized epilepsy not better classified. The sensitivity, specificity, PPV and NPV for photoparoxysmal response for juvenile myoclonic epilepsy and genetic generalized epilepsy are given in Table 4.

3.3. Group C: children with asymmetric photic driving

We identified 24 children (12 boys and 12 girls) with asymmetric photic driving, with ages ranging from 1.5 to 14 y (mean ± SD: 8.0 y ± 4.0 y). MRI data was available for 18 of these children: 11 had normal imaging and 7 abnormal. Of the latter, 5 had focal lesions identified in the same hemisphere in which photic driving attenuation was seen. The two remaining children had either absent or abnormal corpus callosum. Overall, a variety of structural abnormalities, both acquired and congenital, were observed; the full list of diagnoses and structural abnormalities is in Supplementary Table. Table 5 shows the diagnostic value measures for asymmetric photic driving for brain MRI abnormality.

3.4. Group D: children with asymmetric sleep spindles

We identified 30 children (22 boys and 8 girls) with asymmetric sleep spindles, with ages ranging from 2 months to 16 y (mean ± SD: 4.6 y ± 4.8 y). MRI data was available for 29 of these children: 28 had abnormal imaging, with 22 having focal cortical abnormality on the same side as the sleep spindle attenuation. Ten of the patients had a remote history of middle cerebral artery infarction, one of whom had a subsequent hemispherectomy due to drug-resistant epilepsy. The remaining 6 children had diffuse cortical abnormalities that were more prominent on the side of sleep spindle attenuation. A full list of diagnoses and structural abnormalities is in Supplementary Table. Table 5 shows the diagnostic value measures of asymmetric sleep spindles for brain MRI abnormality.

4. Discussion

In this study, we evaluated the diagnostic value of several EEG abnormalities in children, calculating sensitivity, specificity, PPV, and NPV for centrotemporal spikes, photoparoxysmal response, asymmetric photic driving, and asymmetric sleep spindles. These data will aid clinicians in interpreting the clinical significance of these EEG findings in different clinical scenarios. The data are particularly important as the 2022 ILAE position papers have made clear that specific EEG patterns are mandatory criteria in the definition of epilepsy syndromes [20, 21, 22].

Although centrotemporal spikes are classically associated with childhood epilepsy with centrotemporal spikes, a self-limited focal epilepsy of childhood, the PPV and specificity of centrotemporal spikes for childhood epilepsy with centrotemporal spikes or atypical childhood epilepsy with centrotemporal spikes were only 58% (52%–64%) and 70% (61%–77%), respectively. However, if we considered only children with normal development and neurological examination, these measures increased to 75% (66%–81%) and 83% (75%–89%). Other phenotypes in which centrotemporal spikes were observed included focal structural epilepsy and other self-limited childhood epilepsies (Panayiotopoulos syndrome, Gastaut syndrome, and childhood absence epilepsy). Among children with centrotemporal spikes and normal neurological exam at baseline, 22% of children with unilateral centrotemporal spikes compared to 3% in children with bilateral centrotemporal spikes had abnormal brain MRI. Taken together, these findings suggest that while clinicians can reasonably reserve ordering a brain MRI in children with centrotemporal spikes and a classical history for childhood epilepsy with centrotemporal spikes, there should be a low threshold for neuroimaging in those with unexpected clinical findings, particularly if the centrotemporal spikes are unilateral. This is consistent with the 2022 ILAE position paper which considers a causal lesion on MRI to be exclusionary, but notes "An MRI is not required for diagnosis but should be strongly considered in cases with alerts [20]".

For patients with centrotemporal spikes and structural brain abnormalities, most had either congenital malformations or perinatal acquired brain injury. These findings suggest that although centrotemporal spikes may not appear until later in childhood, they reflect an earlier disruption to normal brain development. We did not have access to detailed clinical data regarding prenatal and perinatal care, but these may be important factors in determining which patients go on to develop centrotemporal spikes [23].

Photoparoxysmal response is considered a classical finding in genetic generalized epilepsy, particularly in patients with juvenile myoclonic epilepsy. Given that juvenile myoclonic epilepsy is a subset of genetic generalized epilepsy, it is unsurprising that our data showed that photoparoxysmal response had a higher specificity for genetic generalized epilepsy than for juvenile myoclonic epilepsy; 92% (85%–96%) versus 82% (73%–88%). However, our data found that photoparoxysmal response had a sensitivity of 92% (64%–100%) for juvenile myoclonic epilepsy, much higher than expected given that Wolf and Goosses reported photosensitivity in only 31% of juvenile myoclonic epilepsy patients [24]. Interestingly, we found that 80% of children with photoparoxysmal response without a history of seizures had a family history of epilepsy. This finding of photoparoxysmal response in apparently seizure-free relatives of those with epilepsy is similar to previous reports [25].

An asymmetric photic driving response is usually considered to be a sign of hemispheric dysfunction; however, our data found this to be an unreliable EEG finding, with a sensitivity of only 17% (7%–31%) and a specificity of 80% (68%–90%) for cerebral structural abnormality on MRI. One reason for this may be that asymmetric photic driving can occur due to artifact, particularly if the strobe light is not properly placed,

or the patient does not maintain midline head position and good fixation [26]. When asymmetric photic driving is noted on EEG, the video should be reviewed to assess whether the test was properly performed, or if artifact is a likely explanation. If necessary, photic stimulation should be repeated.

In contrast, asymmetric sleep spindles are a very important finding, having specificity of 98% (88%–100%) for a structural abnormality on brain MRI. The unilateral attenuation of sleep spindles likely indicates severe, diffuse dysfunction of the hemisphere in question. Brain abnormalities identified in our cohort included prior hemispherectomy, remote stroke, previous meningoencephalitis, and abnormal corpus callosum. Neuroimaging should be considered in all patients with asymmetric sleep spindles on EEG, although in many cases these patients will have significant clinical neurological abnormalities so brain MRI may already have been performed.

The findings of this study should be considered with some caution as there are certain limitations. The number of patients in the asymmetric photic driving and asymmetric sleep spindle groups was relatively small, limiting the confidence level in those findings. As well, we used an age-matched cohort of pediatric patients with seizures to allow for calculation of the diagnostic variables. This cohort was drawn from a tertiary epilepsy specialty clinic so may not be representative of pediatric patients who have EEG studies overall. Furthermore, our data were gathered via retrospective chart review, so some clinical data may have been missing or inconsistently documented.

Nevertheless, our data allow for better understanding of the clinical significance of these four EEG findings. More precise clarification of the diagnostic value of these neurophysiologic abnormalities could be achieved with a multi-center prospective study, enrolling all patients referred for EEG at multiple medical centers.

Declarations

Author contribution statement

Mohammed Ashour: Conceived and designed the experiments; Performed the experiments; Analyzed and interpreted the data; Contributed reagents, materials, analysis tools or data; Wrote the paper.

Erica Minato: Analyzed and interpreted the data.

Abdulla Alawadhi, Saoussen Berrahmoune, Elisabeth Simard-Tremblay, Chantal Poulin: Contributed reagents, materials, analysis tools or data; Wrote the paper.

Kenneth A. Myers: Conceived and designed the experiments; Analyzed and interpreted the data; Contributed reagents, materials, analysis tools or data; Wrote the paper.

Data availability statement

Data will be made available on request.

Declaration of interest's statement

The authors declare no conflict of interest.

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