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The influence of EEG-detected nocturnal centrotemporal discharges on the expression of core symptoms of ADHD in children with benign childhood epilepsy with centrotemporal spikes (BCECTS): A prospective study in a tertiary referral center

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ABSTRACT

Benign childhood epilepsy with centrotemporal spikes (BCECTS) is the most frequent benign focal epilepsy in childhood. Although it is described as a benign epilepsy syndrome, many studies have revealed that a significant number of patients have some degree of neuropsychological impairment.

Thirty-two patients with BCECTS aged 6–11 years were included in the study. All patients (without any antiepileptic or psychiatric medication) underwent all-night EEG monitoring and complex neuropsychological testing to diagnose the presence of core symptoms of attention-deficit/hyperactivity disorder (ADHD).

The spike index (number of spikes per minute) on awake and asleep EEG, age at seizure onset, family history of epilepsy, and perinatal risks were correlated with the results of neuropsychological testing.

Of the 32 patients, 21 patients (65.6%) fulfilled the criteria for ADHD diagnosis. Children who were younger at epilepsy onset demonstrated lower IQ and higher attention deficit ($P = 0.004$) and higher impulsivity ($P = 0.016$). The occurence of epileptiform discharges on nocturnal EEG was positively related to higher attention deficit and higher impulsivity.

The findings are discussed in terms of how interictal discharges in the centrotemporal region during sleep affect the development of cognitive functions in children during critical epochs of neuropsychological development.

1. Introduction

Benign childhood epilepsy with centrotemporal spikes (BCECTS) is the most frequent benign focal epilepsy in childhood and represents around 15% to 25% of epilepsy syndromes in children below 15 years of age [1,2]. The age at onset is between 4 and 10 years in 90% of the patients, and the median age at onset is around 7 years. The BCECTS is seen more frequently in males than females, with a ratio of 3:2 [2]. Seizures are clearly related to sleep in 80% to 90% of the patients, but in 10% of the patients, the seizures occur only in waking states [2]. Seizure frequency is usually low; around 10% of cases present only one seizure. The seizures are characterized by hemifacial motor signs, with speech arrest usually preceded by somatosensory signs; seizures often involve the limbs ipsilateral to the involved facial side [2]. Electroencephalogram (EEG) in BCECTS typically reveals specific epileptiform foci characterized by a wide, biphasic spike–wave complex localized in a centrotemporal region, with a normal background [3]. Epileptiform discharges amplify during nonrapid eye movement (NREM) sleep by a factor of two to five times without disturbing sleep organization [1].

Although BCECTS is described as a benign epilepsy syndrome, many studies have revealed that a significant number of patients have some degree of neuropsychological impairment. Despite a favorable seizure outcome and normal intelligence, children with BCECTS often have difficulties in various domains of neuropsychological functioning, such as behavior [4–7], language [8–11], cognition [6,12–16], attention [11,17–20], and memory [11,21], which may lead to learning difficulties [9,22,23]. A prominent comorbidity in children with BCECTS is attention-deficit/hyperactivity disorder (ADHD) [11,15,17–20,24–26]. The prevalence of ADHD in the general population is 3% to 7% [27]; it is 31% in children with BCECTS [15].

Some studies have tried to identify the factors responsible for the development of neuropsychological impairment and especially ADHD

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symptomatology in children with BCECTS. Age at seizure onset, epilepsy duration, impact of AED treatment, etc., have been evaluated, as having the impact of epileptiform discharges, their lateralization, and mainly their sleep activation [19,22,28]. The atypical evolutions of BCECTS – to 'BCECTS plus conditions' such as Landau–Kleffner syndrome, to electrical status epilepticus in slow wave sleep, or to atypical forms of BCECTS which can be present in 1% to 7% of patients [1] – prove that ongoing nocturnal interictal epileptiform activity can influence neuropsychological deficits in children and the severity can depend on the sleep activation of EEG discharges [15].

The aim of our study was to quantify the prevalence of ADHD in children with BCECTS and to analyze the effect of nocturnal epileptiform discharge activation on the development of executive functions and ADHD symptomatology in children with BCECTS. We discuss hypotheses of how sleep disruption interferes with the complexity of specific neuronal networks.

2. Methods

2.1. Participants

This prospective single center study included 52 consecutive children diagnosed with BCECTS at the Brno Epilepsy Center, Department of Pediatric Neurology of the University Hospital Brno between 2008 and 2016. All patients were admitted to the hospital directly after the first epileptic seizure. None of the patients had been diagnosed with ADHD before the manifestation of the first seizure.

Inclusion criteria were the following: a) aged 6–11 years; b) diagnosis of BCECTS made by a board-certified pediatric neurologist based on International League Against Epilepsy (ILAE) criteria [29]; and c) normal neurological examination.

The following exclusion criteria were applied: a) any neurological or psychiatric medication 6 months prior to the diagnosis or during EEG and neuropsychological testing; b) any structural brain magnetic resonance imaging abnormality that could exclude the diagnosis of BCECTS; c) any accompanying neurological disorder; and d) mental retardation (intelligence quotient (IQ) less than 70).

In total, 32 patients of the initial 52 were enrolled in the study; 20 patients were excluded because of improper age, a lack of asleep EEG needed for the evaluation, or incomplete neuropsychological testing.

2.2. EEG

Applying the international 10-20 system, awake and asleep EEG recordings were performed for all patients. Electroencephalogram recordings were obtained before the initiation of antiepileptic drug (AED) or psychiatric treatment. At least 30 min of awake EEG recording consisted of routine activation procedures including eye closing and opening, photic stimulation, and hyperventilation. Asleep EEG was performed as an all-night EEG lasting 6 to 8 h. In BCECTS, the frequency of epileptiform discharges is known to increase upon falling asleep and during the first NREM phase of sleep. To eliminate the impact of this observation resulting in a false higher activation of the epileptiform discharges, we evaluated the asleep EEG throughout the whole night.

The number of interictal epileptiform discharges in the centro-temporal region was manually counted during the whole awake EEG and in ten randomly chosen 20-minute epochs in NREM I–II and NREM III. Patients were divided into three groups according to the laterality of spikes on EEG (left, right, and bilateral).

The spike index (SI) (number of spikes per minute) was calculated during wakefulness, NREM I–II, NREM III, and total NREM sleep. The rate of occurrence of epileptiform discharges on EEG was evaluated by SI differently in the awake and asleep states. An SI lower than 10 was assessed as *low occurrence* during wakefulness; an SI higher than 10 was assessed as *high occurrence*. The border for this assessment during the different sleep phases was 30, with SI under 30 assessed as *low occurence* and SI above 30 as *high occurence*.

2.3. Neuropsychology

Czech versions of standardized neuropsychological batteries were applied to assess the core symptoms of ADHD (attention deficit, hyperactivity, and impulsivity) (Table 1). All neuropsychological testings were performed by a certified child psychologist. The assessment of patients according to the core symptoms of ADHD was established on the basis of a study by McGrew [30].

All patients were AED and psychiatric drug naive at the testing. The Wechsler Intelligence Scale for Children III (WISC III) and its subtests were used for assessing IQ in order to exclude patients with mental retardation (IQ less than 70). The WISC III subtests for Coding, Symbol Search, Letter Number Sequencing, and Labyrinths were used for assessing attention deficit; impulsivity was also evaluated using Labyrinths. A scaled score of 8 or lower (1 standard deviation below the mean) was taken as indicative of attention impairment. The Number Sequencing Test was applied for evaluating attention deficit. A sten score of 4 or less (1 standard deviation below the mean) was taken as indicative of attention deficit. The Trail Making Test was similarly applied for impulsivity. The results of these tests were not directly used to diagnose ADHD or to assess ADHD severity.

The Conners' Parent Rating Scale (CPRS) and the Test Observation Form were used to examine the core symptoms of ADHD. According to the results, subjects were divided into two groups: with ADHD and without ADHD. The T-score border was 60; higher values led to a diagnosis of ADHD.

2.4. Procedures

The patients were admitted to the department after the first seizure. Once the diagnosis of BCECTS has been established, they underwent all-night EEG recording and complete neuropsychological testing. Both examinations were performed within 2–5 days, and all patients were AED and psychiatric drug naïve at the testing.

Age at seizure onset, sex, handedness, family history of epilepsy, and perinatal risks were assessed.

2.5. Statistical analysis

Standard summary statistics were used to express primary data, absolute and relative frequencies for categorical and binary data, arithmetic mean supplied with standard deviation, and median supplied with minimum–maximum range for continuous data.

The statistical significance of the differences among the groups of patients in continuous variables was tested by the nonparametric Mann–Whitney or Kruskal–Wallis test. Robust rank methods were used because assumptions of normality could not be fulfilled in the primary distribution of values.

The degree of relationship between continuous variables was described by Spearman's rank correlation coefficient and its statistical significance.

Analysis was performed in SPSS software 24.0.0.0 (IBM Corporation, 2015).

3. Results

3.1. Baseline data (Table 2)

We studied a group of 32 patients (17 males and 15 females). All patients met the BCECTS criteria according to the 1989 ILAE Classification.

The average patient age at seizure onset was 7.5 ± 1.4 years; median: 8.0 years (6.0; 11.0).