Epilepsy & Behavior 82 (2018) 164–169

Contents lists available at ScienceDirect

Epilepsy & Behavior

journal homepage: www.elsevier.com/locate/yebeh

The relevance of attention deficit hyperactivity disorder in self-limited childhood epilepsy with centrotemporal spikes

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ARTICLE INFO

Article history:
Received 3 October 2017
Revised 13 March 2018
Accepted 13 March 2018
Available online xxxx

Keywords:
Rolandic epilepsy
ADHD
Attention
Executive deficits
Benign childhood epilepsy with centrotemporal spikes

ABSTRACT

In this study, we aimed to evaluate the attentional and executive functions in patients with benign childhood epilepsy with centrotemporal spikes (BCECTS) with and without attention-deficit hyperactivity disorder (ADHD) compared with controls and compared with patients with ADHD without epilepsy. We evaluated 12 patients with BCECTS and ADHD (66.7% boys; mean age of 9.67 years); 11 children with non-ADHD BCECTS (63.6% boys; mean age of 11.91 years); 20 healthy children (75% boys; mean age of 10.15 years); and 20 subjects with ADHD without epilepsy (60% boys; mean age of 10.9 years). We used a comprehensive battery of neuropsychological tests to evaluate attentional and executive functions in their broad domains. Patients with BCECTS and ADHD had worse performance in Conners' Continuous Performance Test II (reaction time standard error [$p = 0.008$], variability [$p = 0.033$], perseverations [$p = 0.044$] and in reaction time interstimuli interval [$p = 0.016$]). Patients with ADHD showed worse performance in Trail Making Test B errors [$p = 0.012$]. In conclusion, patients with BCECTS and ADHD had worse executive and attentional performance compared with controls than non-ADHD patients with BCECTS. Regardless of the presence of epilepsy, ADHD also negatively impacted executive and attentional functions but in different executive subdomains compared with patients with epilepsy.
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1. Introduction

Executive functions (EFs) refer to a set of cognitive and metacognitive functions related to a self-directed behavior [1,2]. These functions are involved in anticipation, organization and planning, sequencing, action initiation, and inhibition of nontarget stimuli and distractors. These also refer to the updating of information, flexibility in changing the action plan, and the monitoring of complex behaviors directed to a goal [1–4]. These are distinct and independent abilities, though closely interrelated. Attentional skills are a key component of EFs since they organize and select the perception of stimuli and actions.

Benign childhood epilepsy with centrotemporal spikes (BCECTS), or rolandic epilepsy, is the most common focal epilepsy of childhood (10–24% of new cases of pediatric epilepsy). Based on the current classification of epileptic syndromes, BCECTS is a focal epilepsy syndrome of unknown etiology [5,6], the onset of which occurs between 6 and 13 years. Benign childhood epilepsy with centrotemporal spikes is usually associated with a good prognosis since seizures remit during adolescence [7].

Although named a benign epilepsy, it is recognized that patients who have this epilepsy have cognitive deficits and psychiatric disorders. Children and adolescents with BCECTS have impairments in different areas of EFs [8–13] and attentional skills [8,14–16]. Also, attention-deficit hyperactivity disorder (ADHD) is the most common psychiatric disorder in BCECTS, manifesting mainly in the inattentive subtype, occurring in 30 to 50% of all patients [17,18]. Its impact on quality of life, social adaptation, and school performance overcomes the relevance of epilepsy per se since 70%–80% present easy-to-control seizures and self-limited epilepsy.

There is an impairment of several domains of executive and attentional functions in BCECTS. Gündüz, Demirbilek, and Korkmaz [10] observed worse performance in children with BCECTS compared with controls using tasks that involved inhibition and selective attention. On the other hand, they found no significant differences in tests that evaluated visual organization and planning. Croona et al. [9], in a sample of 17 patients and 17 controls, described deficits involving verbal fluency, organization, and planning but not in visual and verbal working memory, alternating attention, and sustained attention. Finally, the study of Lindgren et al. [11] demonstrated impairments in verbal fluency, working memory, organization, planning, and inhibition. Several studies demonstrated the presence of impairments at different levels

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https://doi.org/10.1016/j.yebeh.2018.03.017
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of attentional functioning in children and adolescents with BCECTS [12,14,19–24]. Still, there is no consensus about the attentional profile of these children. Some studies have shown impairments of divided attention [14,25] and selective attention/inhibitory control [12,14,16,21,26,27]. There are controversies on sustained attention [14,21,28]. In general, most studies used only one or few instruments to evaluate this domain.

Of note is the overlap between executive/attentional deficits observed in BCECTS and those described in ADHD [29–33]. However, the presence of ADHD and specifically cognitive impairments related to this disorder is usually neglected in studies that address the executive functioning of children with BCECTS. Therefore, it is not possible to determine whether the deficits commonly described in patients with BCECTS are related to epilepsy per se, the psychiatric comorbidity, or both. In this context, it remains to be determined whether there is a particular profile for patients with BCECTS and ADHD compared with patients with BCECTS without ADHD and patients with ADHD without epilepsy.

In this context, we aimed to evaluate the attentional and EFs in patients with BCECTS with and without ADHD and the attentional and executive functioning in patients with ADHD and BCECTS compared with patients with ADHD without epilepsy.

2. Methods

2.1. Subject description

All patients with BCECTS were recruited from the Ambulatory of Epilepsy of the Hospital das Clinicas, Faculty of Medicine, University of Sao Paulo (HCFMUSP)—a tertiary care center for epilepsy diagnosis and treatment. We only included patients whose parents agreed to this protocol. For this study, we included only patients with a typical or classical electroclinical profile of BCECTS. Therefore, we included patients with brief, focal hemifacial seizures consisting of unilateral facial sensorimotor symptoms, oropharyngolaryngeal manifestations, speech arrest, and hypersalivation. These seizures rarely evolved to bilateral tonic–clonic seizures and were sleep-related. Electroencephalography (EEG, current or previous) had blunt high-voltage centrotemporal sharp waves, often followed by slow waves that were activated by sleep (doublets and triplets) and tend to shift or spread from side to side. These epileptiform discharges had the negative pole maximum in the centrotemporal regions and the positive pole maximum in the frontal regions [34]. The clinical data of these patients are shown in Supplementary Material 1.

We obtained a detailed history of epilepsy from parents and caregivers. This information was corroborated by medical files and personal contact with referring physicians.

All patients underwent a prospective EEG and video-EEG (VEEG) evaluations, with a minimum duration of 1 h. All EEGs performed previously were considered for analysis if the recording was obtained with the same technical parameters. All EEGs were obtained during wakefulness, drowsiness, and spontaneous sleep after sleep deprivation. Scalp electrodes were placed according to the 10–20 or 10–10 system. One board-certified neurophysiologist analyzed EEG tracings.

2.1.1. Group I: patients with BCECTS

We categorized children and adolescents with BCECTS into two groups according to their psychiatric evaluation: BCECTS with ADHD and BCECTS without ADHD.

The subgroup of patients with BCECTS and ADHD was composed of 12 patients. Eight were male (66.66%), with a mean age of 9.67 years (standard deviation (SD): 2.38) and 4.25 years of schooling (SD: 2.70), and nine (75%) of them attended private schools. The estimated IQ was 102.33 (SD: 14.77). Nine children (75%) had the inattentive type, one (8.3%) was hyperactive, and two (16.6%) had combined ADHD. Three patients had a diagnosis of ADHD preceding the seizure onset.

Eleven patients composed the subgroup of patients with non-ADHD BCECTS. Seven were male (63.63%), with a mean age of 11.91 years (SD: 1.75) and 6.82 years of schooling (SD: 1.83), and five (45.45%) attended private schools. The average IQ was 100.09 (SD: 15.81).

2.1.2. Group II: patients with ADHD without BCECTS

Patients with ADHD, matched by age, gender, and years of education, were recruited from the Ambulatory Building of ADHD — Hospital das Clinicas, Faculty of Medicine, University of Sao Paulo.

We included 20 subjects with ADHD. Twelve (60%) were male, with a mean age of 10.9 years (SD: 2.46), 5.9 years of formal education (SD: 2.44), and an average IQ of 102.33 (SD: 14.77). According to the psychiatric evaluation, seven patients (35%) presented the inattentive type, two (20%) had the hyperactive type, and nine (45%) had combined ADHD.

2.1.3. Group III: control group

We included 20 healthy children without learning disabilities or neurological and psychiatric disorders. Healthy controls had the same educational and social background and were matched for age, gender, and number of years of education. Fifteen (75%) were male, with an average age of 10.15 years [SD: 2.54], 5.25 years of education [SD: 2.71], and an average IQ of 105.95 [SD: 10.66]. Seventeen of them studied in private schools (85%).

We excluded patients and controls with an estimated IQ lower than 80, who had a diagnosis of a psychiatric disorder (other than ADHD), who abused alcohol or drugs, who had any surgical brain interventions (including epilepsy surgery), and had a lack of school attendance. Clinical signs of drug intoxication or any other condition that could lead to cognitive impairment other than epilepsy in the patient group was also an exclusion criterion. We also excluded patients with epilepsy presenting with moderate/severe learning disabilities that might impair neuropsychological performance. We excluded patients with ADHD and BCECTS using psychoactive drugs (e.g., methylphenidate). In the groups of patients with drug-resistant BCECTS, the time elapsed between the last seizure and the moment of the neuropsychological evaluation was at least 48 h.

2.2. Instruments

2.2.1. Psychiatric evaluation

The same child psychiatrist performed the clinical psychiatric evaluation, followed by a structured interview (Kiddie-SADS-PL instrument — Schedule for Affective Disorders and Schizophrenia for School-Aged Children — 6–18 years) [35]. Patients were classified according to the categorical classification of the Diagnostic and Statistical Manual of Mental Disorders, 4th Edition (DSM-IV) [36].

2.2.2. Neuropsychological evaluation

For this study, we used a comprehensive battery of neuropsychological tests to evaluate attentional functions and EFs in their broad domains.

The tests used to measure executive and attentional functions [37–43] are shown in Fig. 1.

2.3. Statistical analysis

Numerical data are described as mean and standard deviation whereas categorical variables as absolute and relative frequency. Comparison of demographic data (age, gender, type of school, and education) and IQ scores among the four groups was assessed with analysis of variance (ANOVA) model and chi-square test (N — 1 variation).

Neuropsychological performance was compared among groups with a full factorial two-way ANOVA model or a generalized linear model (GLM) for families Poisson, negative binomial or gamma with the

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