Epilepsy & Behavior 37 (2014) 54–58

Contents lists available at ScienceDirect

Epilepsy & Behavior

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

Attention-deficit/hyperactivity disorder and attention impairment in children with benign childhood epilepsy with centrotemporal spikes

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ARTICLE INFO

Article history:
Received 15 February 2014
Revised 25 May 2014
Accepted 27 May 2014
Available online 27 June 2014

Keywords:
Benign childhood epilepsy with centrotemporal spikes
Benign rolandic epilepsy
Attention-deficit/hyperactivity disorder
Attention impairment

ABSTRACT

Attention-deficit/hyperactivity disorder (ADHD) is a common comorbidity in children with epilepsy and has a negative impact on behavior and learning. The purposes of this study were to quantify the prevalence of ADHD in benign childhood epilepsy with centrotemporal spikes (BCECTS) and to identify clinical factors that affect ADHD or attention impairment in patients with BCECTS.

The medical records of 74 children (44 males) with neuropsychological examination from a total of 198 children diagnosed with BCECTS at Asan Medical Center were retrospectively reviewed. Electroclinical factors were compared across patients with ADHD and those without ADHD. Mean *T*-scores of the continuous performance test were compared across patients grouped according to various epilepsy characteristics.

Forty-eight (64.9%) patients had ADHD. A history of febrile convulsion was more common in patients with ADHD than in patients without ADHD ($p = 0.049$). Bilateral centrotemporal spikes on electroencephalogram were more common in patients receiving ADHD medication than in patients with untreated ADHD ($p = 0.004$). Male patients, patients with frequent seizures prior to diagnosis, and patients with a high spike index (≥40/min) on sleep EEG at diagnosis had significantly lower visual selective attention ($p < 0.05$).

Children with BCECTS had a high prevalence of ADHD, and frequent seizures or interictal epileptiform abnormalities were closely related to impairment of visual selective attention in children with BCECTS, indicating the need for ADHD or attention impairment screening in children with BCECTS.

1. Introduction

The prevalence of behavioral and cognitive problems such as attention-deficit/hyperactivity disorder (ADHD) is higher in children with epilepsy than in children with other chronic illnesses and children in the general population [1,2]. Inattention and hyperactivity are the most common clinical complaints of children presenting with epileptic epilepsy syndromes [2,3]. Attention deficits in children with epilepsy are influenced by multiple factors, including the neurological and seizure status, medication, and various environmental factors. Impaired attention and concentration negatively impact learning and mental development [4,5]; therefore, early diagnosis and appropriate treatments of attention problems in children with epilepsy are very important.

Benign childhood epilepsy with centrotemporal spikes (BCECTS), or benign rolandic epilepsy, is the most common childhood epilepsy syndrome and accounts for 15–25% of epilepsy diagnoses in children younger than 15 years of age [6]. Benign childhood epilepsy with centrotemporal spikes classically occurs in neurologically and cognitively healthy children, and the presentation is usually a nocturnal partial seizure with a typical electroencephalogram (EEG) that shows centrotemporal spikes (CTSs) [6]. Although BCECTS is considered a benign form of childhood epilepsy, formal neuropsychological evaluations have revealed a higher prevalence of cognitive impairment in children with BCECTS than in healthy sex- and age-matched children [7]. In the last two decades, a wide spectrum of neuropsychological and learning disabilities such as speech and language disorders, reading disabilities, attention impairment, visuomotor and behavior impairments, and psychiatric problems including aggression and oppositional behavior have been reported in children with BCECTS [8–12].

Attention-deficit/hyperactivity disorder is also considered as a comorbidity associated with BCECTS by interference, based on some studies [13–15]. However, the incidence of ADHD in BCECTS and the causes of this comorbidity remain unclear. Besides, it is uncertain which epilepsy characteristics (seizure frequency, epileptic discharges, or age at seizure onset) cause the negative neuropsychological consequences that impact attention.

The purposes of the present study were to quantify the prevalence of ADHD in children with BCECTS and to evaluate the associations

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http://dx.doi.org/10.1016/j.yebeh.2014.05.030
1525-5050/

between epilepsy factors and ADHD/attention impairment in patients with BCECTS.

2. Materials and methods

2.1. Participants

One hundred and ninety-eight children were diagnosed with BCECTS at Asan Medical Center Children's Hospital from 2007 to 2012 and followed for at least 1 year after diagnosis. The clinical diagnosis of BCECTS was confirmed by pediatric neurologists according to the International League Against Epilepsy classification. The following exclusion criteria were applied: (1) age younger than 2 years or older than 16 years at diagnosis; (2) diagnosis of any epilepsy other than BCECTS; (3) any brain magnetic resonance imaging abnormality that could affect the diagnosis of BCECTS; (4) any accompanying neurologic disorder such as cerebral palsy, neurometabolic disease, or mental retardation (intelligence quotient < 70); and (5) follow-up duration for less than 1 year after diagnosis. Among the 198 children, however, 124 children were not enrolled in this study as their parents refused a neuropsychological assessment for the reasons of negative attitude or unrecognized necessity. In the end, 74 children who received a neuropsychological examination by neuropsychologists were eligible for the study and formed the study sample.

2.2. EEG recordings

Electroencephalogram recordings were obtained before the initiation of antiepileptic drug (AED) treatment. All subjects underwent EEG recording during wakefulness and/or sleep. At least 30 min of digital recording were obtained using the international 10–20 system for electrode placement. Routine activation procedures including hyperventilation, eye closure, and photic stimulation were performed if possible. Sleep EEGs were recorded until induction of stage II sleep was confirmed by the technician. Sleep EEGs were obtained from 71 patients among the 74 patients. All EEG records were evaluated by three board-licensed pediatric neurologists (TS Ko, MS Yum, and EH Kim). The number of CTSs was manually counted, and the amplitude of the most active individual epileptic spike on visual inspection was measured. The spike index (number of spikes per minute) during wakefulness and sleep was calculated, and spikes with amplitude ≥ 200 μV were defined as high-amplitude spikes.

2.3. Evaluation of attention impairment

Selective and sustained attention impairments were evaluated using a computerized continuous performance test (CPT) [16]. The Korean version of the CPT has been standardized, and its validity and reliability have been established [17]. The four variables quantified were omission errors (failure to respond to the target), commission errors (erroneously responding to a nontarget), response times (RTs) for a correct target, and the standard deviation (SD) of the RTs. Only 49 patients could perform the CPT before receiving the ADHD medication, and the attention score was presented with *T*-scores adjusted for age. A *T*-score of 65 (1.5 SD above the mean) or greater was taken as indicative of attention impairment. These results of the CPT were not directly used to diagnose ADHD or assess ADHD severity.

2.4. Procedures

All data were retrospectively retrieved from electronic medical records. The clinical variables recorded were age at the onset of seizures, history of febrile convulsions, family history of epilepsy, seizure type, seizure frequency in the year prior to diagnosis, number of AEDs, response to first AED, duration of medical therapy, duration of follow-up, the control of seizures at follow-up (complete or incomplete), and the presence or absence of ADHD and comorbidities such as tic disorder, oppositional or conduct disorder, anxiety, depression, and learning disabilities. Attention-deficit/hyperactivity disorder was clinically diagnosed by a pediatric psychiatrist based on the *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition* (*DSM-IV*) criteria of ADHD: the diagnosis of ADHD was made if more than six out of nine symptoms of inattention or hyperactivity–impulsivity had persisted for at least six months, using the questionnaire of ADHD symptoms for parents.

2.5. Data analysis

All statistical analyses were performed using SPSS statistical software, version 18.0 (SPSS, Inc., Chicago, IL). Clinical and EEG variables were compared across patients with BCECTS with ADHD and patients with BCECTS without ADHD and across patients with BCECTS with treated ADHD and patients with BCECTS with untreated ADHD using independent *t*-tests for continuous variables and χ^2 and Fisher's exact tests for categorical variables. The CPT outcomes (*T*-scores for omission errors, commission errors, RTs, and RT SD) were compared across sex, seizure onset age (<7 or ≥7 years), number of seizures in the year prior to diagnosis (<4 or ≥4), seizure control at follow-up, responses to monotherapy, CTS amplitude (<200 or ≥200 μV), unilateral or bilateral CTSs, a spike index during wakefulness (<10 or ≥10/min), and a spike index during sleep (<40 or ≥40/min) using independent *t*-tests. A $p < 0.05$ was considered statistically significant.

3. Results

3.1. Characteristics of patients with BCECTS

The clinical characteristics of the 74 children with BCECTS are shown in Table 1. The mean age was 10.9 (range = 6.5–16.5) years. The mean duration of follow-up was 3.0 (range = 1.0–6.2) years. At final follow-up, 69 (93.2%) patients were being treated with AEDs: 54 patients were being treated with monotherapy, and 15 patients were being treated with polytherapy. The mean duration of medication was 2.3 (range = 0.2–6.5) years. The most common AED was oxcarbazepine (n = 52, 75.4%), followed by lamotrigine (n = 13, 18.8%). Of the 74 patients with BCECTS, 48 (64.9%) were diagnosed with ADHD. Additional comorbid neuropsychiatric problems were present in 15 (20.3%) patients: tic disorder, n = 7; oppositional defiant disorder or conduct disorder, n = 4; anxiety disorder, n = 2; depressive disorder, n = 1; language disability, n = 1; and adjustment disorder, n = 1. Electroencephalogram background rhythm was normal for age in all patients. The EEG findings are shown in Table 2.

3.2. Association between ADHD and electroclinical characteristics in patients with BCECTS

Clinical characteristics and EEG findings were compared between patients with ADHD and those without ADHD (Tables 1 and 2). The history of febrile convulsions was the only factor that was significantly different between groups ($p = 0.049$; Table 1). Of the 48 patients diagnosed with BCECTS and comorbid ADHD, 14 (29.2%) received pharmacotherapy for ADHD (methylphenidate, n = 8 and atomoxetine, n = 6). On the assumption that patients with severe ADHD received pharmacologic treatment, we compared the clinical characteristics and EEG findings across patients with BCECTS with treated comorbid ADHD and patients with BCECTS with untreated comorbid ADHD. Bilateral CTSs were more frequent in treated patients than in untreated patients ($p = 0.004$), but all other clinical variables were similar in the two groups (Table 3).