Epilepsy & Behavior xxx (2015) xxx–xxx

Contents lists available at ScienceDirect

Epilepsy & Behavior

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

Targeted Review

Cognitive and behavioral outcomes in benign childhood epilepsy with centrotemporal spikes

Jennifer Vannest *, Jeffrey R. Tenney, Rose Gelineau-Morel, Thomas Maloney, Tracy A. Glauser

Cincinnati Children's Hospital Medical Center, USA

ARTICLE INFO

Article history:
Revised 28 January 2015
Accepted 30 January 2015
Available online xxxx

Keywords:
Benign childhood epilepsy with centrotemporal spikes
Rolandic epilepsy
Cognitive outcomes
Behavioral outcomes
Antiepileptic drugs

ABSTRACT

We review the evidence that BECTS may be associated with cognitive dysfunction and behavioral problems, the extent to which these problems may be associated with patterns of EEG abnormalities in BECTS, and the impact of antiepileptic medication on cognition and behavior in BECTS.

A growing literature examining cognitive and behavioral outcomes suggests that children with BECTS perform below the level of their peers. Consistent with this, neuroimaging studies reveal that BECTS has an impact on structural and functional brain development, but the potential influence of frequency and lateralization of centrotemporal spikes (CTS) on cognition and behavior is not well understood. Treatment with AEDs is an option in BECTS, but existing studies have not clearly shown a clear relationship between elimination of CTS and improved cognitive or behavioral outcomes.

Key questions

1. What is the evidence that BECTS is associated with cognitive dysfunction and behavioral problems?
2. Are EEG abnormalities associated with cognitive dysfunction and/or behavioral problems in BECTS?
3. Does antiepileptic medication impact cognitive dysfunction and/or behavioral problems in BECTS?

1. Introduction

About 15% of all children with epilepsy have benign childhood epilepsy with centrotemporal spikes (BECTS) [1]; its incidence is 6.2–21 per 100,000 children aged 15 years or younger [2]. Children with BECTS have "brief, simple, partial, hemifacial motor seizures frequently having associated somatosensory symptoms; these seizures have a tendency to evolve into grand mal seizures… often related to sleep. Onset occurs between the ages of 3 and 13 and seizures resolve by age 15–17 years" [3]. Seizures are relatively infrequent: most patients (60–70%) have 2 to 10 total, and 10–20% may have only one. The classic EEG shows frequent "blunt high-voltage centro-temporal spikes (CTS), often followed by slow waves that are activated by sleep and tend to spread or shift from side to side". Benign childhood epilepsy with centrotemporal spikes is traditionally assumed to have a relatively benign course with likely cessation of seizures by adulthood, regardless of seizure frequency [1,4–7]. However, during the time that children have seizures and CTS, the brain is continuing to develop both structurally [8–10] and functionally [11–14], and BECTS may alter this development. Specifically, a number of recent studies have documented cognitive and/or behavioral problems in children with BECTS [15–40]. In this review, we present (1) the evidence that BECTS may be associated with cognitive dysfunction and behavioral problems, (2) the extent to which this may be associated with patterns of EEG abnormalities in BECTS, and (3) the impact of antiepileptic medication on cognition and behavior in BECTS.

2. What is the evidence that BECTS is associated with cognitive dysfunction and behavioral problems?

2.1. Language and cognition

General intellectual function (full-scale IQ) is typically normal in BECTS [36,38,41,42]; poorer, but normal range, performance in children with BECTS compared to controls has been observed in a few studies [34,43]. In a majority of studies, problems are observed in specific cognitive domains. Studies examining standardized language and verbal memory outcomes [17,27,34–38] have shown that patients with BECTS perform more poorly than age-matched healthy controls. In one of the largest studies, Jurkeviciene et al. [21] assessed language function in 61 children with BECTS and 35 controls. Children with BECTS performed more poorly than controls on verbal fluency, speeded

* Corresponding author at: Pediatric Neuroimaging Research Consortium, Cincinnati Children's Hospital Medical Center, 3333 Burnet Avenue, ML 5033, Cincinnati, OH 45229-3039, USA. Tel.: +1 513 636 6959; fax: +1 513 636 3754.
E-mail address: Jennifer.Vannest@cchmc.org (J. Vannest).

http://dx.doi.org/10.1016/j.yebeh.2015.01.041
1525-5050/

naming, and instruction comprehension tasks, with earlier age of onset (but not duration of epilepsy) associated with lower language scores. Overvliet et al. noted that 23% of 48 children with BECTS had a history of speech therapy and that 35% repeated a year in primary school, significantly more than the general population; they suggest that language deficits may appear as a precursor to the diagnosis of BECTS [44]. Some studies have found these language deficits in contrast to normal nonverbal abilities [37,38]; but more frequently, nonverbal performance was also found to be lower than that in controls [17,34–36].

Consistent with these findings, other studies have documented lower performance among patients with BECTS on visuospatial tasks and nonverbal memory [15,33,41,45,46] (see also [31] for a review of memory studies in BECTS). Attention and inhibition problems have also been reported. For example, Deltour et al. found that 29 children with BECTS performed lower than expected norms on a Continuous Performance task as well as a color/word Stroop task [47]; this study and others revealed poorer performance on auditory attention and inhibition subtests of the NEPSY [32,47,48]. Most recently, Kim et al. have reported a much higher incidence of ADHD in 74 children with BECTS compared to that in the general population [49]. These language and cognitive problems impact academic achievement: Piccinelli et al. report that early onset of BECTS is associated with specific learning disabilities in reading, writing, and calculation [36]; subsequent studies have confirmed these educational difficulties [42], particularly in reading [19,44].

We note that while this literature suggests that language and cognitive problems are prevalent in BECTS, they are also common in childhood epilepsy more generally. Similar patterns of mild cognitive impairment have been observed in children with new-onset epilepsy; Hermann et al. [50] found that regardless of epilepsy syndrome, school-age children with new-onset epilepsy scored more poorly than controls across cognitive domains. Fastenau et al. [51] found similar results in a large group of children with a first-recognized seizure; however, cognitive deficits were more likely in children with multiple seizures, those taking antiepileptic drugs, those with epileptiform activity on EEG, or those with symptomatic/cryptogenic etiology. Another large clinical cohort study [52] found that over 50% of children with epilepsy had an IQ lower than 80 and that the duration of epilepsy and number of seizures in the previous year were associated with lower IQ; however, this did not apply to idiopathic epilepsy. Consistent with our summary of BECTS studies above, they suggest that children with idiopathic epilepsy may have a profile of specific cognitive deficits that are not apparent on tests of general intelligence. Indeed, Masur et al. [53] found that 36% of children with childhood absence epilepsy exhibited attention problems, while general intelligence and scores in other domains were in the normal range. They found that attention ultimately impacted memory, executive function, and academic achievement. This suggests that specific epilepsy syndromes may be associated with a particular neurocognitive profile, which in the case of BECTS, is characterized by normal-range IQ but difficulties in particular domains.

2.2. Behavioral and psychiatric comorbidities

Behavior problems have also been consistently observed in studies of children with BECTS. Using parent and teacher interviews and the standardized Child Behavior Checklist (CBCL), Volkl-Kernstock et al. [34] reported that children with BECTS show a significant deficit in the ability to recognize and express interpersonal relations and that their teachers complained about disturbing behavior. On the CBCL, parents reported significantly greater aggressive behavior, attention problems, and anxiety/depression in children with BECTS compared to healthy controls. In a larger study of 43 patients, Samaitiene et al. [39], also conducting parent report using the CBCL, found that children with BECTS had significantly greater aggressive behavior, social problems, attention problems, and anxiety/depression than controls, though these findings were only significant in a group of patients with BECTS who were treated and had an average duration of epilepsy of over two years. In this same group, age of onset was associated with greater report of delinquent behavior on the CBCL, and withdrawn and delinquent behavior scores were increased with greater duration of epilepsy. In a follow-up study with 61 patients with BECTS, Samaitiene et al. [40] found that only patients who had had seizures over the preceding 6 months had higher CBCL scores for aggressive behavior, social problems, attention problems, and anxiety/depression than healthy controls, and these behavioral problems were also related to sleep problems. Similarly, Eom et al. [20] also found that children with BECTS showed internalizing behavior problems on the CBCL in the borderline and clinical range.

As in the case of language and cognitive problems described above, behavior problems in pediatric epilepsy may not be unique to BECTS; in a large epidemiological study, Davies et al. [54] reported a 37% rate of emotional or behavior disorders in children with epilepsy, based on parent interview. In a sample of 300 children with at least a single seizure, Austin et al. [55] found that behavior problems were more likely in children with seizures compared to their siblings with no seizures, though behavior problems decreased over a 36-month period. A greater incidence of behavior problems was associated with lower processing speed scores and a number of social/family variables. When viewed in combination with the studies of BECTS reported above, these behavioral problems may be more persistent in children with BECTS than in children with epilepsy in general, but there may be a greater association with age of onset and duration of epilepsy, though direct comparisons between epilepsy syndromes are not available.

The specific profiles of these reported cognitive and behavioral/psychiatric problems suggest the possibility of an identifiable pathophysiological basis. Studies investigating this pathophysiology have begun, mostly through the use of noninvasive neuroimaging methods.

2.3. Neuroanatomical changes and functional reorganization associated with BECTS

Corresponding with these cognitive and behavioral changes are changes in functional and structural neuroanatomy in patients with BECTS. Multiple studies have found functional changes specifically involving language networks. One study [23] found a lesser degree of left lateralization for language function during covert verb generation with visual stimulus presentation in patients with BECTS compared to controls. A similar pattern of atypical lateralization in the anterior language network was also observed by Datta et al. [18], using an fMRI sentence generation task. Most recently, atypical (more rightward) lateralization in patients with BECTS using a semantic decision task was observed by Vannest et al. [30] (see Fig. 1); this study also showed a more posterior shift of language-related activation in patients with BECTS during a story listening task. Monjauze et al. [56] recorded event-related potentials during an auditory verb generation task. They found that patients in remission from BECTS had atypical lateralization in frontal regions as well as significant language deficits. Similarly, in patients with BECTS with unilateral CTS present during sleep, an asymmetry of the auditory event-related potential (compared to controls) was observed contralateral to the side of the epileptiform activity, and this was accompanied by poorer language scores [22].

Besseling et al. used functional MRI (fMRI) to visualize abnormal integration between the motor and language systems [57] in children with BECTS and also demonstrated abnormal connectivity between the sensory–motor networks [58]. In a follow-up study, they also described a reduced structural connectivity to functional connectivity correlation in the centrotemporal and medial parietal networks, suggesting delayed maturation of the structural and functional network convergence that occurs in normal development, which may contribute to cognitive and language deficits in patients with BECTS [59]. Other studies also point to aberrant functional and structural maturation of the brain in patients with BECTS. Oser et al. demonstrated decreased

Please cite this article as: Vannest J, et al, Cognitive and behavioral outcomes in benign childhood epilepsy with centrotemporal spikes, Epilepsy Behav (2015), http://dx.doi.org/10.1016/j.yebeh.2015.01.041