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Does the Epileptic Side (Left, Right, Bilateral) Differently Impair the Cognitive Functioning in Patients with Benign Childhood Epilepsy with Centro-Temporal Spikes (BECTS)? A Literature Review

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Abstract

In Canada, Epilepsy affects approximately 3 to 6 per 1000 children between the ages of 0 and 15. Of these children, 15-25% suffer from benign epilepsy with centro-temporal spikes (BECTS), making BECTS the most common benign childhood focal epileptic syndrome. Impact of the side of epileptic foci on cognitive development however remains unclear. Among 269 articles from 1806 to 2016 reviewed, 17 articles have specifically addressed the impact of the side of epileptic foci on the cognitive functioning. Our review suggests that the epileptic side is more deleterious to cognitive functions specifically sub served by the same hemisphere. However, for reasons that remain unclear, other cognitive functions may also be affected. We recommend that these children benefit from a neuropsychological follow-up.

Keywords: Benign childhood epilepsy with centrotemporal spikes; BECTS; Benign rolandic epilepsy; Cognitive deficits; Neuropsychology; Epileptic focus

Introduction

BECTS is classified as a benign syndrome, cognitive and behavioral impairments have consistently been demonstrated during the active phase and after remission [1-3]. Benign epilepsy with centrotemporal spikes BECTS (also called rolandic epilepsy) is an age-dependent neurological disorder, with an onset between 3 and 13 years of age and affects roughly 0,5% of previously healthy and neurologically intact children [4-8]. In 75% of BECTS cases, the disorder appears between the ages of 7 and 10, with a 1.5 male predominance [9]. Typically, seizures resolve after puberty [10]. Epileptic seizures in BECTS are caused by the hyperexcitability of neurons in the somatosensory or somatomotor system [11]. In 75% of BECTS patients, seizures only occur during sleep, predominantly during non-rapid eye movement (NREM) sleep, while falling asleep or during awakening. About 20% have interictal activity or several seizures during the day. BECTS was long considered a benign syndrome as compared to other types of epilepsy since remission occurs during adolescence and owing to the preservation of global cognitive abilities, which were often within the normal range following remission [1, 6,12,13]. However, cognitive and behavioral disorders are more and more documented in this population [1-3]. Recent reports demonstrate neurocognitive impairments at epilepsy onset, which could persist following remission [14]. Studies on typical BECTS often report general cognitive deficits and behavioral disabilities which impact quality of life [3,10,15-20]. More specifically, several authors have reported language related deficits in this population, and even propose the consideration of this syndrome to be part of the selective language impairments spectrum [20-24]. However, many studies, most of them reviewed in the recent literature review by Malfait and Lippe [25], highlight the great heterogeneity of neuropsychological delays and deficiencies amongst BECTS children. Causes of this heterogeneity are unclear. One possibility is that localization of epileptic foci could account for differences in neuropsychological profiles. BECTS is considered a focal epilepsy syndrome, presenting with left or right lateralized seizures, however bilateral seizure focus can also be present. Few authors report their findings according to lateralization of epileptic foci. This paucity of reports may be due to a lack of statistical power in studies. Furthermore, epileptic focus can travel from one hemisphere to the other during a BECTS patient history, which complicates focus lateralisation labelling. Moreover, as in other epilepsy syndromes, genetic background and brain development play a significant factor in the mobility of seizure focus and therefore the interpretation of causes related to cognitive impairments [9].

As such, the aim of the present review is to describe the cognitive deficits found specifically in left BECTS, right BECTS and bilateral BECTS in order to better understand the differential impact of seizure focus lateralization on cognitive deficits.

Methods

The studies reviewed were taken up until the 24th of June 2016 by searches from Ovid (Ovid MEDLINE(R) 1946 to June 2016, Eric 1965 to June 2016, and PsycINFO 1806 to June 2016, Web of Science and Proquest Dissertations and Thesis. We reviewed articles published in English and French with the following isolated or combined key words search:

- Epilepsy, rolandic epilepsy, rolandic spikes, centrotemporal spikes, centro temporal spikes, benign rolandic epilepsy, benign partial epilepsy of childhood, benign childhood epilepsy with centro temporal spikes, benign childhood epilepsy with centrotemporal spikes, benign epilepsy with centro temporal spikes, benign epilepsy with centrotemporal spikes, benign epilepsy of childhood with rolandic spikes, benign focal childhood epilepsy, idiopathic epilepsy syndrome, idiopathic rolandic epilepsy, idiopathic focal epilepsy with centrotemporal spikes, idiopathic focal epilepsy with centro temporal spikes, typical benign rolandic epilepsy, partial benign epilepsy, BFCE, BECTS, BCECTS, BECRS, BRE.
- Cognitive deficit, cognitive impairment, cognitive dysfunction, cognitive process, cognitive ability, cognitive skill, executive function, cognitive assessment, neuropsychological, intellectual function, intellectual development, cognitive development, intellectual disability, metacognition, cognitive disorder, mental disorder, memory, brain disorder, psychiatric disorder.
- Left hemisphere, right hemisphere, cerebral cortex, corpus collosum, interhemisphere, inter hemisphere, cerebral dominance, lateral dominance, left brain, right brain, temporal lobe and lateralization.

Abstracts from 817 articles and manuscripts (446 from Medline 1945 - now, 173 from Eric and PsycINFO 34 from Web of Science and 162 from Proquest Dissertations and Thesis) were carefully read. References of selected articles and manuscripts were also inspected. Only manuscripts and articles addressing cognitive and behavioral impairments in BECTS children with a description of epileptic focus were included in this review. Out of 267 articles and 1 thesis of interest, the final number of studies reporting significant effects of seizure focus lateralization was limited to 17 (Table 1).

Study	Population (epileptic focus)	Age when tested (years.months)	Number of control participants M (mean) [age range]
Bedoin et al.	18 (9 L / 9 R / 0 B)	m L = 9.3; m R = 9.1	54 (Each patient matched with 3 controls for age and sex)
Riva et al.	24 (8 L / 16 R / 0 B)	[7-12.6]; m = 9.5	16 ; [7.5-13]; m = 10
Bulgheroni et al.	24 (13 L / 7 R / 4 B)	[7-12.6]; m = 9.5	16 ; [7.5-13]; m = 10
Metz-Lutz et al.	22 (11 L / 9 R / 2 B)	[4.3-11.1]; m = 7	No
Bedoin et al.	12 (6 L / 6 R / 0 B)	m = 10.2	12 Matched
Piccirilli et al.	22 (14 L / 8 R)	[9-13]; m = 11.5	15 Matched
Hommet et al.	23 (8 L / 12 R / 3 B)	[16-28]; m = 20.2	33 Healthy control (m = 20); 10 seizure free (m = 21)
Monjauze et al.	13 (4 L / 3 R / 5 B / 1 DNA)	[15-23.8]	13 Matched [15.1-21.2]
Beaumanoir et al.	10 (3 L / 7 R)	m = 8	6
Duman et al.	13 (11 L / 8 R / 2 B)	[7-12.2;] m = 8.9	21 Matched [7.5-12.1], m = 9.4
D'Alessandro et al.	44 (18 L / 11 R / 15 B)	[9-13]; m = 10.7	9 [9-13]; m = 11
Liasis et al.	12 (5 U / 3 Bi)	[6-12]	12 Matched
Piccirilli et al.	43 (14 L / 14 R / 15 B)	[9-13]; m = 10.8	15 Matched
Pinton et al.	18 (3 L / 9 R / 4 B / 2 DNA)	[4.2-8.10]; m = 6.8	No
Bedoin et al.	30 (18 L / 12 R / 0 B)	m L = 9.1; m R = 9.5	Matched respectively with 18 and 12 controls for age and gender
Monjauze et al.	16 (5 L / 5 R / 6 B)	[6-15]; m = 12.2	No
Fonseca et al.	42 (17 L / 17 R / 8 B)	[8-11]; m = 9.6	42 Matched

Abbreviations: BECTS = Benign epilepsy with centro-temporal spikes; **Bi** = Bilateral; **L** = Left ; **R** = Right; **B** = Bilateral; **U** = Unilateral; **M** = Mean; **SD** = Standard deviation; **m** = mean age; **U** = Unilateral; **[ ]** = age range.

Table 1: Population of the 17 articles reviewed.

In this review, all 17 neuropsychological studies will be synthesized by reporting results per epileptic focus (left, right, and bilateral), in order to shed light on potential specific cognitive profiles in BECTS (Table 1). Furthermore, results of other studies will be discussed in the context of absence of lateralization effects.

Do children with left-sided BECTS focus experience specific cognitive impairments related to left hemisphere functions

Language disorders are commonly reported in BECTS children both during the active phase and after remission. As expected, children with a left-sided focus experience a wide range of language processing deficits (criterion: at least -1 σ or -2 σ on the standardized subtests), at

both early stages (e.g. discrimination), or at more advanced stages (e.g. sentence comprehension and reading) of language processing.

Dichotic listening tasks have been used to specifically study epilepsy side effects on auditory-verbal processing lateralization. Bedoin et al. [26] reported anomalies in lateralized auditory processing using a dichotic listening task (see methodology [27]). They found that the typical right ear advantage in dichotic listening tasks was significantly diminished in left BECT children compaired to right BECTS and control children. Authors proposed that epileptic discharges in the left hemisphere hinder the development of the specialized area of auditory processing. In accordance with this interpretation, Riva et al. [28] found inferior performances in phonemic fluency, in addition to a diminished mental lexicon and lexical access in left BECTS children. Consistently, Metz-Lutz et al. [29] found that during the active period, 4 children on 11 with a left-sided focus had a low memory span in the auditory-verbal modality.

Furthermore, right hemifield facilitation for reading was not found for children with a left-sided focus (Bedoin et al. [27]). Indeed, these children did not demonstrate a better performance in reading when the stimuli were presented to the right visual hemifield, compared to the children with right-sided focus and controls. This specific pattern of language lateralization have already been assessed by Piccirilli et al. [30] who investigated language lateralization with a dual-task procedure [31] involving the performance of two concurrent tasks (speech and right or left motor task) in order to create interference between both tasks, especially when the right motor task is being performed. In children with left-sided focus, no difference was observed between their right and left hand, which is interpreted as a different (i.e., bilateral) language organization, compared to both the control group and children with the right-sided focus, who had the same pattern of results. In contrast, the right-sided focus BECTS showed less productive right finger tapping under the verbal task; a demonstration of normal left language lateralization. Similarly to this study, Hommet et al. [32] studied language lateralization using a dual-task procedure and found similar results with specific deficits for left sided focus BECTS, compared to right BECTS, children with generalized epilepsy and controls.

On the contrary, however, Bulgheroni et al. [33] found that children with BECTS did not show the same pattern of results as control children in a Vowel-consonant dichotic listening test (DLT) [34], but independently from the lateralization of epileptic foci. Indeed, typical language lateralization demonstrates a right ear advantage/left hemisphere advantage. However, children with BECTS, regardless of the hemisphere in which the epileptic focus was located, did not show any ear advantage. These results suggest a bilateral representation of the auditory input, i.e. phonological processing of auditory and verbal stimuli (speech perception).

Brain imaging studies have investigated language organisation directly. Several studies find atypical cerebral organisation for language in BECTS without any impact of the side of epileptic foci [3,22,35]. Similar to Lillywhite et al. [36], Datta et al. [37] show in BECTS patients atypical bilateral language activation, for sentence generation and reading, with no difference between the patients with right or left sided focus. Moreover, some studies on reading using EEG have highlighted atypical patterns of brain activations across the scalp [38]. Our recent study found typical organization of reading during fMRI recording, but compensatory Bold responses in intensity and additional brain regions (p.ex putamen) [25]. However, due to small sample sizes these studies did not show distinct cerebral responses patterns between right and left sided focus BECTS.

However, with similar sample sizes, Monjauze et al. [38] studied left-sided focus children in remission (medication-free and seizure-free for at least 1 year), paired with matched controls. They found that the expressive language performances of children with left focus on the initial EEG were lower than these of children with right or bilateral focus. In ERP, the control group demonstrated a normal left frontal lateralization but in almost all the children with BECTS, there was a right frontal lateralization. According the authors, this could reflect a greater involvement of the right frontal lobe in the BECTS group.

Right hemisphere dysfunctions in left BECTS: Deficits normally found in individuals with right hemisphere lesions have been demonstrated in children with a left-sided focus, such as deficits in the visuo-spatial domain perception and visuomotor skills. Duman et al. [39] performed a prospective study on [11] newly diagnosed and unmedicated children in the active phase of BECTS as compared to matched controls. Children with left focus showed lower performances on the visuo-motor abilities and a lower N2P3 amplitude at fronto-central Fz recording site than children with right focus and controls. This lower N2P3 amplitude demonstrated disorders in visual-motor coordination. However, the authors precisely emphasize that the right hemisphere normally supports these functions and more than 5 errors in the Bender Test indicate the possibility of suffering from right hemisphere impairments rather than left hemisphere impairments. The authors explain these results by a possible shifting of the epileptic focus in time that hindered the right hemisphere. In fact, left and right focus children can suffer from similar cognitive deficits as it is demonstrated in the study of D'Alessandro et al. [40], who studied 18 right-handed children with left-sided focus, 11 with right-sided focus, 15 with a bilateral foci and 9 control children. All were seizure-and medication-free for at least 6 months before the neuropsychological assessment. In general, children with left-sided focus performed less well on verbal tasks, but both left and right focus children demonstrated difficulties in the visuomotor tasks. Another study of Liasis et al. [41] demonstrated impairments in the early language functioning in 12 patients with BECTS, without medication, who were seizure free for at least one month, compared to 12 matched controls. In all patients with a unilateral focus (left or right), Liasis et al. [41] identified a language processing dysfunction, and a more pronounced difficulty when the auditory discrimination was in noise compared to quiet. They also noted abnormal auditory processing (P85-120 – N1) ispilateral to the hemisphere with the predominant focus.

In sum, children with left-sided focus suffer from specific cognitive impairments especially in the verbal domain, as could be expected from people suffering from left brain injuries. However, left focus children seem to encounter disabilities in the visuo-spatial domain, as would be expected in children with right focus. We propose that a left focus can hinder left brain activity and therefore cognitive functions generally supported by the left hemisphere. Recruitment of other brain regions seems to occur, but compensation effects are not totally effective. Importantly, BECTS patients, including children with left seizure focus tend to show executive dysfunctions which impacts on several other cognitive processes (i.e., motor inhibition, response organization, impulsivity and sustained attention) [42].

Do children with right-sided BECTS focus experience specific cognitive impairments related to right hemisphere function

Expected cognitive impairments of right-sided brain dysfunction have been shown in BECTS children. The pioneer study addressing this matter is from Beaumanoir et al. [42]. Out of 10 children with BECTS, 2 patients with right-sided focus had lower performances on the Bender Visual Motor Gestalt Test, which is a brief test of visual-perceptual abilities, visual-motor skills and memory [43]. Consistent with Beaumanoir et al. [42], Piccirilli et al. [44] investigated « right hemisphere » functions in [43] children with BECTS (seizure free for at least 6 months) paired with 15 matched controls. There were 14 children with left-sided focus, 14 with right-sided focus, and 15 with a bilateral focus. They found right-side epilepsy focus children were significantly more impaired then left sided and bilateral BECTS children at visual attention and visuo-spatial orientation judgement. In a prospective research with a follow-up of 18 months, Metz-Lutz et al. [29] studied 22 patients with BECTS. Nine had a right focus and 2 a bilateral focus. As expected, they found that during the active period, the 5 children with right-sided focus had low visuo-spatial memory span. Pinton et al. [45] performed a retrospective study on 18 children with typical BECTS, in which 9 of them had a right-sided focus. Qualitatively, authors found that performances from right-sided focus children were particularly low for non-verbal tasks. Bedoin et al. [46] prospectively studied 30 right-handed children with typical BECTS. In their evaluation of lateralized visuo-spatial attention, they found more errors in performances from right-sided focus children when the left visual hemifield contained stimuli. The authors suggest that these children demonstrate a unilateral deficit when they have to disengage their attention from the right visual hemifield in favor of the left, a deficit more pronounced when these children demonstrated comorbid ADHD. Taken together, studies tend to demonstrate that right-sided BECTS children have greater impairments than other BECTS children on visual attention and visuo-spatial orientation tasks, but these deficits may be augmented with ADHD comorbidities.

Left hemisphere dysfunctions in right BECTS: However, some studies demonstrate that children with right-sided focus can also have impaired cognitive functions which are normally observed in patients with left hemisphere injuries. In the prospective research of Metz-Lutz et al. [29] children with a right-sided focus showed lower performances on a verbal recognition test and sequential processing. They also assessed the integrity of the frontal lobes with the executive function tasks in 13 children with BECTS, and found impaired functioning of inhibition and control. Interestingly, in the later study, children with right and bilateral focus were more prone to cognitive deficits.

Monjauze et al. [47] demonstrated that the performances in reading and spelling were equivalent for the children with left or right-sided focus. Nevertheless, there performances were inferior to those of children with bilateral foci. Riva et al. [28] show that children with right-sided focus obtained lower performances in expressive language, more precisely in lexical capacities involving semantic knowledge, compared to controls. In this study, the presence of multifocal spikes correlated with more pronounced deficits in semantic knowledge and lexical comprehension. For those authors, increased temporal spikes were generally associated with a less efficient cognitive level and impairments in several language tasks.

In summary, data from studies presented here suggest that children with right-sided focus BECTS suffer from specific cognitive impairments, normally supported by the cerebral areas concerned, but also from more extended cognitive deficits.

Do children with bilateral BECTS foci experience specific cognitive impairments related to both hemispheres

Two studies suggest bilateral BECTS children show greater cognitive impairments compared to unilateral BECTS children. Studies report significantly greater cognitive impairments in bilateral BECTS children in subtests administered to evaluate mental flexibility, visuomotor skills and oral and written language capacities compared to left BECTS, right BECTS and control children [40,46]. Moreover, laterality indexes calculated from brain responses to a verbal dichotic listening task suggest children with bilateral foci show less hemispheric speech lateralisation compared to children with a unilateral focus33. In contrast, other studies found bilateral BECTS to be more similar to controls than unilateral BECTS [45]. For example, event related potentials brain responses related to auditory processing were found to be similar to controls in bilateral BECTS children as opposed to unilateral BECTS [41].

Discussion

Although BECTS is still officially considered as a benign syndrome with mild cognitive impairments, more and more studies highlight the existence of a wide range of cognitive deficits associated to it [48]. From the studies reviewed, some cognitive deficits related to the hemisphere in which the epileptic focus is located emerge. Reorganisation of brain networks to reach normal cognitive functioning despite the epilepsy does not seem to be fully efficient in this population. Impairments could be caused by ipsilateral dysfunctioning but also by a crowding effect in other brain regions. This could help explain why cognitive functions normally subserved by the hemisphere contralateral to the epilepsy focus may also be impaired in this population. One example reported in this review is D'Alessandro et al. [40] study, where both left and right foci children demonstrated difficulties in the visuomotor tasks. Another example cited above is the study of Liasis et al. [41] which demonstrated in all BECTS patients with a unilateral focus (left or right), language processing dysfunction and a more pronounced difficulty when the auditory discrimination was in noise compared to quiet. Those results were also reflected through the abnormal auditory processing (P85-120 – N1) ipsilateral to the hemisphere with the predominant epileptic focus.

Nevertheless, our review provides evidence that, in BECTS, children with left-sided focus experience greater difficulties than children with a right or bilateral epileptic focus and control children for the cognitive functions that are normally sustained by the left hemisphere. As reviewed above, children with a left epileptic focus have more difficulties or show developmental disorders regarding auditory-verbal memory [29], expressive language [38], verbal tasks [40], and phonemic fluency [28]. Of course, this pattern is not perfect since visuo-spatial motor abilities [39] and digital recognition [42] were also greatly affected. Recent studies have shown that children with left sided BECTS present with a bilateral pattern of language organization [30,35] with the loss of the expected pattern of right visual advantage/left hemisphere language lateralization [27] and a less important right ear advantage during verbal tasks [26].

In contrast, children with a right-sided epileptic experience greater difficulty than BECTS children with a left or bilateral epileptic focus and control children for the cognitive functions that are normally sustained by this right hemisphere. As we have previously mentioned, BECTS children with a right epileptic focus have more difficulties or show developmental disorders regarding visuo-spatial motor abilities [42], visuo-spatial memory, visuo-spatial processing attention and judgment of spatial orientation of the items [24], non-verbal tasks [45]. But they also show deficits in sequential processing, attention, verbal recognition [29], morphosyntactic abilities [47], and expressive language, particularly in lexical capacities [28]. Overall, these children demonstrate a loss of the expected pattern of left visual advantage/right hemisphere visuo-spatial lateralization and the loss of the classic global superiority effect demonstrating a higher cost for the left visual hemifield and a unilateral deficit to disengage attention from the right to the left visual hemifield [27,29,46].

However, regardless of the laterality of the epileptic focus, children with BECTS show a language processing dysfunction on several neuropsychological tests and an abnormal auditory processing ispilateral to the hemisphere with the predominant focus, further reflected in the brain electrical activity (EEG) [41]. Furthermore, Monjauze et al. [47] found that performances in reading and spelling were equivalent for the children with left or right-sided focus but inferior to those of children with bilateral focus. In children with BECTS, regardless of the hemisphere in which the epileptic focus was located, there was no ear advantage as is expected in typical language lateralization (right ear advantage/left hemisphere advantage) [33]. In children with bilateral focus, some studies found no particular deficits [41], while other studies found specific impairments in attention [29], reading and language capacities such as in discrimination of words and lexical decision [49].

The importance of language deficits in this population is stricking, but its specific causes remain unclear since it surpasses the epileptic focus localisation. In fact, several studies have not found seizure focus lateralization effects on cognitive processes [3,22,35]. As it is more and more recognized in most pediatric pathologies in the litterature, we can posit an interplay between genetic and environmental influences during the perinatal period [9], problems of cell migration explaining a potential epileptic susceptibility and an immaturity of brain structure aggravated [50] by epileptic discharges causing a neurodevelopmental delay. Further studies are necessary to isolate factors that directly or indirectly influence the nature and the persistence of cognitive deficits, such as those cited previously. Longitudinal studies are needed to determine how benign this disease really is, during the active phase as well as after remission.

Moreover, this broad spectrum of cognitive deficits may be conjointly caused by other factors, although these factors are not yet fully identified in the literature. Discordance in results could come from the fact that unilateral epilepsies can evolve towards shifting focus with time and spread of abnormal activity is very frequent. As such, classification criteria may vary from study to study, creating heterogeneity. In some studies, cognitive deficits could be correlated with frequency of spikes in the EEG [3,45] with interictal seizures [51-53] and with the epileptic locus and its potential spread [54]. Interestingly, in recent studies [55], cognitive deficits such as impulsivity [56] were linked to disturbances in the maturation of the frontal and prefrontal volumes, further associated with the length of the epileptic active period, the frequency of spike-waves and the frequency of seizures. In addition, cognitive deficits may be related to sleep disturbances, themselves caused by AEDs side effects or discharges during sleep that fragment it. Sleep disturbances leads to impairments of wakefulness and alertness during the day [57-59].

In conclusion, it is difficult to isolate the factors that can lead to the modification of the neuropsychological profile over time [28]. Indeed, the discordance of the cognitive impairments obtained in these studies can also be explained by several methodological limitations: small sample sizes [24], the absence of an age-and-gender matched control group, as well as the criterion used for defining a difficulty or a deficit (e.g. - 2 α from the normal range). Some factors such as handedness of the participants and lateralization of their cognitive functions, socioeconomic level and environment, academic skills [60] as well as male / female ratios can have an influence. Moreover, several clinical factors can have an impact, such as age at onset, time since the date of diagnosis and initiation of medication, type of medication (molecule and dosage), number and frequency of seizures, their exact area and spread, structural brain abnormalities, comorbidities, genetic factors, affective and emotional state, and the shift of the epileptic locus in time (location, lateralization of the seizures and their possible spread to other brain areas). The most predominant risk of suffering from neuropsychological impairments found in the literature is the interictal abnormalities and their persistence in EEG [61]. In future studies, these factors will have to be seriously considered, in a large sample size, in order to isolate and understand their potential and relative impacts.

Conflict of Interests

We attest that all coauthors have read and agreed to the content of the manuscript. The authors included in this publication report no conflict of interests in the production of this manuscript.

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