Clinical evaluation of attentional processes in children with benign childhood epilepsy with centrotemporal spikes (BCECTS)

Laëtitia Deltour, Véronique Quaglino, Marion Barathon, Alain De Broca, Patrick Berquin

ABSTRACT – The aim of this study was to identify the attentional processes specifically affected in children with benign childhood epilepsy with centrotemporal spikes (BCECTS). The impact of several factors - laterality of discharges, age-at-onset and duration of epilepsy, and medication - on these cognitive functions was also studied. A group of 29 children with BCECTS was evaluated using standardized tests performed in routine clinical practice and specifically designed to assess executive and attentional functions. This group obtained mean scores significantly lower than normative means specifically for tasks involving attention control processes, i.e. cognitive flexibility and inhibitory processes. Neither the epilepsy-related factors that we studied nor the medication appeared to influence performance of these tasks. These data suggest an impact of BCECTS on attentional processes, the most affected being attention control processes that develop late.

Key words: benign childhood epilepsy with centrotemporal spikes, Rolandic epilepsy, cognitive development, attention, executive functions

According to recent reviews, children with epilepsy have an increased risk of attentional problems (Sanchez-Carpintero and Neville 2003, Schubert 2005, Dunn and Kronenberger 2006). Attention is essential for academic achievement as it allows control of all other cognitive functions and improves the efficiency of processing. Attention is a complex cognitive function composed of several interacting processes. Although no consensus has been reached in this field, in clinical practice, the evaluation includes generally sustained attention, corresponding to the capacity to maintain a certain level of efficiency over time, and selective attention, corresponding to the capacity to select relevant information from various distractors. Atten-
tion control is ensured by executive functions, in particular inhibition and cognitive flexibility processes (Rebok et al. 1997, Klenberg et al. 2001), which are also evaluated. Executive functions, essential for new or complex situations, also comprise other functions, such as planning and problem solving (Welsh et al. 1991).

Benign childhood epilepsy with centrotemporal spikes (BECTS) is the most frequent of the idiopathic partial epilepsy syndromes, with an onset between the ages of two and 13 years. BECTS is associated with a favorable prognosis (Bouma et al. 1997), as seizures usually resolve at adolescence. However, the "benign" nature of BECTS has been called into question due to the learning disabilities and subtle cognitive deficits frequently reported in this population (Nicolaï et al. 2006, for a review). Various degrees of impairment of certain language functions (Staden et al. 1998, Monjauze et al. 2005, Northcott et al. 2005, Papavasiliou et al. 2005), visuo-motor coordination and visuo-spatial capacities (D’Alessandro et al. 1990, Pinton et al. 2006, Völkl-Kernstock et al. 2006), learning and memory (Croona et al. 1999, Metz-Lutz et al. 1999, Northcott et al. 2005) have been reported. Several studies have also reported difficulties in the tests evaluating executive and attentional functions in children with BECTS (Gündüz et al. 1999, Chevalier et al. 2000, Pinton et al. 2006, Deltour et al. 2007). However, most of these studies did not specifically evaluate the various executive and attentional functions (Sanchez-Carpintero and Neville 2003). Prospective studies systematically investigating various aspects of these functions need to be conducted. The most extensively studied hypothesis concerning factors responsible for cognitive disorders in BECTS is the impact of epileptiform abnormalities. Several studies suggest a link between the presence of right-sided discharges and impairment of cognitive functions associated with the right hemisphere, such as visuo-spatial capacities or sustained attention (D’Alessandro et al. 1990, Piccirilli et al. 1994, Massa et al. 2001, Bedoin et al. 2006). However, other studies did not show any correlation between laterality of discharges and cognitive deficits (Weglage et al. 1997, Northcott et al. 2005). Age-at-onset of seizures and duration of epilepsy also appear to be two possible causal factors for cognitive deficits. Attentional and executive processes do not all have the same developmental trajectory (Klenberg et al. 2001). The prefrontal areas and the functions associated with these areas, such as attention control processes, do not reach maturity before early adulthood (Huttenlocher et al. 1982, Williams et al. 1999, Bedard et al. 2002). Executive and attentional functions are therefore still in the process of development at the time of onset of BECTS. The deficits potentially observed might therefore differ according to the age-at-onset of seizures and the duration of the epilepsy.

This study was designed to identify the executive and attentional processes specifically affected in children with BECTS, using tests routinely performed in clinical practice and which are specifically designed to evaluate these functions in children. The second objective was to determine whether there is a link between clinical factors (discharges laterality, age-at-onset of seizures and duration of epilepsy) and executive and attentional deficits. Most studies do not support a relationship between antiepileptic monotherapy and the development of neuropsychological disorders (D’Alessandro et al. 1990, Piccirilli et al. 1994, Deonna et al. 2000, Pinton et al. 2006). However, in order to attribute more reliably the observed deficits to epilepsy per se, we checked for the absence of significant differences between children with and without AED.

Methods

Subjects
Twenty-nine children (13 boys, 16 girls) with BECTS, aged 6-12 years (m = 8.7; SD = 1.4) participated in this study. All attended regular classes. The parents of each participant signed an informed consent form after the study had been explained to them and the study was approved by the local ethics committee.

The diagnosis of BECTS according to the ILAE classification, and based on clinical history and recent EEG recordings, was confirmed in each child in a pediatric neurology unit. At the time of diagnosis, EEG demonstrated centrotemporal biphasic spikes. To be included in the study, children had to have a normal neurological and neuroradiological examination. The absence of intellectual deficiency was confirmed by the neuropsychological assessment (Full Scale IQ [FSIQ] estimate > 70 with a French version of the Wechsler Intelligence Scale for Children – Third Edition [WISC-III]; m = 99.7 ; SD = 16.2). Exclusion criteria were as follows: concomitant neurological or psychiatric disorders, sensorimotor deficits, prior neurosurgical intervention, neurological medication other than AEDs and/or combination therapy (two or more AEDs).

Clinical and electroclinical characteristics of the study population are summarized in table 1. Age-at-onset of seizures was between two years six months and nine years 11 months (m = 6.5 ; DS = 1.9). Duration of epilepsy was between one and 89 months at the time of this study (m = 26.8 ; DS = 24.9). None of the children had frequent seizures. Seventeen children had not experienced a seizure for at least six months and the other children experienced their last seizure one month before the study.

Twenty children were treated with single-agent therapy: sodium valproate (n = 10), carbamazepine (n = 4), oxcarbazepine (n = 3) or gabapentin (n = 3). The Mann-Whitney non-parametric test indicated that the mean FSIQ of children taking AEDs (m = 100.3 ; DS = 16.9) was not significantly different from the mean FSIQ of children not taking AEDs (m = 98.3 ; DS = 15.4).

Intercital waking EEGs were performed for each child either on the same day or on the previous or following...
days of this study (± 1 month). A nocturnal EEG was performed in 15 patients.

Materials and procedure

Children were evaluated individually in two sessions at an interval of less than ten days. Standardized tests were performed by the same examiner and under similar conditions. All are validated tests with normative means and standard deviations based on large populations of children. Sequential and simultaneous information processing was evaluated using a French version of the Kaufman Assessment Battery for Children (K-ABC; Kaufman and Kaufman 1993).

In the Sequential Processing Scale, the child solves tasks by arranging the stimuli in a sequential or serial order. This scale is composed of three subtests designed to assess short-term memory, also called attentional capacity: Hand Movements, Number Recall and Word Order. The first subtest also requires cognitive flexibility capacities and the last subtest requires interference resistance capacities.

In the Simultaneous Processing Scale, the child solves spatial or analogical tasks by simultaneously integrating and synthesizing information. This scale is composed of five subtests. The Gestalt Closure subtest measures the visual-perceptual capacities. The Triangles and Matrix Analogies subtests are designed to evaluate the spatial construction and the non-verbal reasoning, respectively. The Spatial Memory subtest assesses the visuospatial short-term memory or the visual modality of attentional capacity; this subtest also requires interference resistance capacities.

Table 1. Clinical and electroclinical characteristics of the population and FSIQ values (m = 100; SD = 15).

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<th>Age ± 1 month</th>
<th>Sex</th>
<th>Education level</th>
<th>Age at 1st seizure ± 1 month</th>
<th>Duration of epilepsy*</th>
<th>EEG focus side</th>
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Mean: 8.7; SD: 1.4

KG 3: year 3 kindergarten (5-6 years); CP: reception (6-7 years); CE1 and CE2: 1st and 2nd year primary (7-9 years); CM1 and CM2: 1st and 2nd year junior (9-11 years); °: repeating of a year; *: in months; **: in years; VPA: sodium valproate; CBZ: carbamazepine; OXC: oxcarbazepine; GBP: gabapentin.
capacities. The Photo Series subtest is supposed to evaluate temporal organization capacities, but raises several methodological problems and was therefore not included in the battery.

The French version of the Stroop Color Word Test (SCWT; Albaret and Migliore 1999) was used to assess inhibitory processes, more specifically the interference sensitivity in serial verbal reactions.

The three attentional and executive functions subtests of the French version of the NEPSY, a Developmental Neuropsychological Assessment (Korkman et al. 2003), were also proposed. The Tower subtest is designed to evaluate the executive functions of planning and problem solving.

The Auditory Attention subtest (Part A of the Auditory Attention and Response Set subtest of the NEPSY) is a continuous performance test designed to measure the ability to attend selectively to linguistic stimuli during a monotonous task; it therefore requires selective and sustained attention. The Auditory Response Set subtest (Part B of the Auditory Attention and Response Set subtest of the NEPSY) also evaluates cognitive flexibility and distractor resistance capacities. The Visual Attention subtest is a cancellation test, which assesses visual selective and divided attention on two more or less difficult parts.

The Continuous Performance Test version 2 (CPT-II; Conners 2003) is a Go-NoGo computerized task lasting 14 minutes. This task is designed to measure sustained attention and prepotent response inhibition capacities. Several indicators of performance in T-scores are calculated; the higher the score, the greater the subject’s difficulties. The main indicator of prepotent response inhibition capacities is the number of commission errors, and the main indicator of sustained attention capacities is the reaction time block change score.

Data analysis

Data analysis was performed with STATISTICA 6.1 Software.

The Student’s t test was used to compare observed and theoretical means on each standardized test. A Spearman correlation test was performed to determine whether there was any correlation between age-at-onset of the seizures or duration of epilepsy and performance in the various cognitive tests. The Mann-Whitney, non-parametric test for independent samples was used to compare children with an earlier-onset of epilepsy with children with a later-onset epilepsy by assigning children to two groups: greater than and less than the median. The same test was used to compare children with and without AEDs and children with paroxysmal discharges predominantly on the right and children with paroxysmal discharges predominantly on the left side.

An alpha risk level of 0.05 was used for all comparisons in this study, but only correlations significant at an alpha level of 0.01 will be presented below.

Results

Analysis of the EEGs performed closest to the neuropsychological assessment showed focal epileptiform discharges in 16 patients, predominantly lateralized to the right in five patients and to the left in 11 patients. Two of the 15 nocturnal EEGs were normal.

The mean results of standardized tests and the p values comparing group means with normative means are presented in table 2.

Neuropsychological assessment with K-ABC

The mean score of the Sequential Processing Scale in the group of 29 children was significantly lower than the theoretical mean (t(28) = -2.21, p < 0.03), due to significantly lower mean scores for Hand Movements (t(28) = -2.1, p < 0.04) and Word Order (t(28) = -3.78, p < 0.0007) subtests. The mean score of the Simultaneous Processing Scale was not significantly different from the theoretical mean, but the mean score of the Spatial Memory subtest was significantly lower than the theoretical mean (t(28) = -2.17, p < 0.04).

Children taking AEDs had a significantly poorer performance than children not taking AEDs on the Sequential Processing Scale (m = 88.15; SD = 18 and m = 102.5; SD = 13.9, respectively; U = 46.5, p < 0.04), and particularly on the Number Recall subtest (m = 87.5; SD = 3.9 and m = 12.1; SD = 3.7, respectively; U = 48, p < 0.05).

No other statistically significant difference was observed between these two groups.

The K-ABC subtests scores were not significantly different between children with discharges predominantly on the right and children with discharges predominantly on the left side.

Age-at-onset of seizures correlated significantly with performance on the Sequential Processing Scale (r = 0.50, p < 0.005), particularly with the Number Recall subtest scores (r = 0.55, p < 0.002). For the Simultaneous Processing Scale, only the Spatial Memory subtest scores were significantly correlated with age-at-onset of seizures (r = 0.61, p < 0.0005). In line with these results, children with an earlier-onset of seizures had a significantly poorer performance than children with a later-onset of seizures on Number Recall (m = 8.21; SD = 4.08 and m = 11.27; SD = 3.61, respectively; U = 58.5, p < 0.04) and Spatial Memory (m = 7.93; SD = 2.06 and m = 10.07; SD = 2.28, respectively; U = 46, p < 0.01) subtests only.

Duration of epilepsy correlated significantly with performance on the Simultaneous Processing Scale (r = -0.61, p < 0.0004), particularly with the scores for the Triangles (r = -0.55, p < 0.002) and Matrix Analogies (r = -0.62, p < 0.0003) subtests. Results obtained on the subtests of the Sequential Processing Scale did not correlate significantly with the duration of epilepsy.
Six children were unable to perform the SCWT because they were too young (n = 4) or had reading difficulties (n = 2). This test was therefore performed in 23 children in whom the mean results were significantly lower than the theoretical mean for the reading (t(22) = -4.06, p < 0.0005) and interference (t(22) = -3.77, p < 0.0001) conditions. The mean score on the designation condition was within the normal range.

Children taking AEDs had a significantly poorer performance than children not taking AEDs in the reading condition of the SCWT (m = -1.18; SD = 1 and m = -0.12; SD = 0.9, respectively; U = 21.5, p < 0.04), but not in the other two conditions.

The NEPSY subtests were performed by all 29 children. Only the mean score of the Auditory Attention and Response Set subtest (t(28) = -3.28, p < 0.003) was significantly lower than the theoretical mean. This was because of a significantly lower mean score on the Auditory Attention part B of the previous subtest (t(28) = -5.17, p < 0.00002). No statistically significant difference was observed between children with or without AEDs for the NEPSY subtests.

Scores for the SCWT and NEPSY subtests were not significantly different between children with discharges predominantly on the right and children with discharges predominantly on the left side. Age-at-onset of seizures and duration of epilepsy did not correlate significantly with the results obtained for these tests. No statistically significant difference was observed between children with an earlier-onset of seizures and children with a later-onset of seizures.

### CPT-II

Twenty-seven children performed the CPT-II (two children did not complete the task). This group obtained significantly higher mean score than the theoretical mean, for omissions (t(26) = 2.82, p < 0.009) and for commissions (t(26) = 2.21, p < 0.04). The mean reaction time (RT) was also significantly longer than the theoretical mean (t(26) = 2.87, p < 0.008). A strong correlation was demonstrated between RT scores and omission scores (r = 0.90, p < 0.0000001), while RT scores and commission scores did not correlate significantly. The mean reaction time block change score was in the normal range.

Children taking AEDs made significantly more omission errors and were significantly slower than children not taking AEDs (omission errors: m = 59.06; SD = 10.42 and m = 48.31; SD = 7.97, respectively; U = 33, p < 0.04). The mean reaction time (RT) was also significantly slower than the theoretical mean (m = 59.39; SD = 10.68 and m = 49.38; SD = 11.4, respectively; U = 37, p < 0.04). Children with discharges predominantly on the right were not significantly different from children with discharges predominantly on the left for the CPT-II.

Age-at-onset of seizures correlated significantly with omission error scores (r = -0.47, p < 0.01) and RT (r = -0.48, p < 0.01). No other statistically significant correlation was observed between age-at-onset of seizures and CPT-II results. In line with these results, children with an

<table>
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<th>p value</th>
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<th>Mean (SD)</th>
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<td>50.37 (6.79)</td>
<td>ns</td>
</tr>
<tr>
<td>Interference RTs°</td>
<td>-0.58 (0.74)</td>
<td>0.001</td>
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</tr>
</tbody>
</table>

* standard scores with m = 10, SD = 3; ** standard scores with m = 100, SD = 15; ° z-scores with m = 0, SD = 1; † T-scores with m = 50, SD = 10; SeqPS: Sequential Processing Scale; SimPS: Simultaneous Processing Scale.
earlier-onset of seizures were significantly slower than children with a later-onset of seizures (RT: m = 60.88; SD = 7.65 and m = 52.29; SD = 13.39, respectively; U = 46, p < 0.03). Duration of epilepsy did not correlate significantly with CPT-II results.

Discussion

The purpose of this study was to evaluate executive and attentional functions in children with BCECTS. The impact of several factors (laterality of discharges, age-at-onset of seizures, duration of epilepsy, and medication) on these functions was also studied.

This group of children with BCECTS presented low scores on the Auditory Response Set subtest of the NEPSY and on the interference condition of the SCWT. In the CPT-II, the commission error score was also higher than the normative mean. This pattern of performance is suggestive of poor cognitive flexibility and interference resistance capacities in this group. This profile could explain why the present study group presented low scores for the Hand Movements, Word Order and Spatial Memory subtests of K-ABC, but not on the Number Recall subtest. These four subtests are designed to assess short-term memory or attentional capacity, but the first three subtests also require cognitive flexibility and interference resistance capacities. Our results support the hypothesis of less efficient attention control in children with BCECTS, a hypothesis previously proposed by several authors (Metz-Lutz et al. 1999, Chevalier et al. 2000). Other studies in children with BCECTS have reported poor cognitive flexibility and divided attention capacities, as evaluated by the Trail Making Test or two targets cancellation tasks (D’Alessandro et al. 1990, Piccirilli et al. 1994, Baglietto et al. 2001). Inhibition difficulties, tested by SCWT or Go-GoNoGo tasks, have also been reported in this population (D’Alessandro et al. 1990, Gündüz et al. 1999, Chevalier et al. 2000, Baglietto et al. 2001) together with difficulties of resistance to interference from distractors (Deltour et al. 2007).

The present study group did not present any deficit in sustained attention, as measured by the Auditory Attention subtest of NEPSY and the CPT-II (indicator of RT block change), or in selective attention, as measured by the Auditory Attention and Visual Attention subtests of NEPSY. These results suggest that children with BCECTS may experience difficulties specifically with tasks involving attention control processes. The mean score of the Tower subtest of NEPSY was also within the normal range, suggesting that the executive functions of planning are preserved in our group. However, in routine clinical practice, this subtest appears to have a weak sensitivity to planning difficulties. So, the use of other tests, such as the Tower of London, may probably lead to different results; planning difficulties evaluated with this test have been reported in children with BCECTS (Croona et al. 1999).

The study population also presented slow reaction times and a high omission error score on the CPT-II. This performance profile had already been observed in children with BCECTS using another computerized task (Deltour et al. 2007). However, the slowness and the predominance of errors of omission have also been reported in children with various types of epilepsy (Mitchell et al. 1992, Oostrom et al. 2002). This result suggests that this performance profile is not specific to children with BCECTS.

The impact of several epilepsy features on the various cognitive functions tested was also studied.

Duration of epilepsy does not appear to have any significant impact on the executive and attentional functions evaluated in this study. The results of the various tests used did not correlate significantly with the duration of the epilepsy. Only performance on the Triangles and Matrix Analogies subtests of K-ABC, which require the spatial constructive capacities and the non-verbal reasoning, correlated with this factor. Völkl-Kemstock et al. (2006) showed that children with BCECTS were not significantly different from controls on the Triangles subtest, while children with BCECTS had a poorer performance than controls on the Matrix Analogies subtest, although their scores remained within the normative mean. These authors did not study the impact of the duration of epilepsy. According to our results, duration of epilepsy could have a negative impact on the development of non-verbal capacities (spatial construction and reasoning).

A negative impact of age-at-onset of seizures on scores of the Number Recall and Spatial Memory subtests, assessing short-term memory or attentional capacity, has been highlighted. Although discordant results have been reported in the literature, the visual modality of these functions has been found, as suggested in our study, to be more frequently impaired than the auditory modality (Metz-Lutz et al. 1999, Baglietto et al. 2001). However, these studies did not evaluate the impact of age-at-onset of seizures. Our results suggest the presence of short-term memory or attentional capacity limitation, regardless of the modality, in children with earlier-onset of seizures. Age-at-onset of seizures does not appear to influence the development of other executive and attentional processes. Children taking AEDs also presented significantly lower scores on the Number Recall subtest than children not taking AEDs. This result could be explained by the fact that the children on AEDs presented an earlier age-at-onset of seizures than children not on AED. Northcott et al. (2005) found that memory span, evaluated by the Digit Span subtest of WISC-III, was preserved and they did not observe any impact of medication on this function. This result could constitute an argument in favor of the impact of age-at-onset of seizures on cognitive performance.

A negative impact of age-at-onset of seizures on RTs and the omission errors score of the CPT-II was also observed. However, children on AEDs were significantly slower and
made more omission errors than children not on AEDs. Consequently, our results cannot identify whether slowness is due to epilepsy, more particularly to age-at-onset of seizures, and/or to medication. However, the study by Northcott et al. (2005) indicated an impact of medication on processing speed, which suggests that this factor probably is involved in slowness. Study of the impact of laterality of discharges on the type of cognitive deficits observed has often led to inconsistent results. Some studies have shown that children with a right-sided or bilateral focus present more attention problems than children with a left-sided focus (D’Alessandro et al. 1990, Piccirilli et al. 1994). We could not corroborate this finding in our study group, as we did not find any significant difference in the tests used between children with discharges predominantly on the right and children with discharges predominantly on the left side. Several explanations for these results can be proposed. Firstly, the group of children with discharges predominantly on the right was very small and no child with a bilateral focus was included in the study. Secondly, and possibly more importantly, the inconsistency of the results between studies can be explained by the fact that BCECTS is not associated with a fixed epileptogenic focus (Gibbs et al. 1954, Dalla Bernardina 1975). To address this issue, it would be interesting to ask children to perform cognitive tests during an EEG examination.

Others studies have demonstrated a correlation between the frequency of epileptiform discharges on waking and/or sleep EEGs and cognitive difficulties (Weglage et al. 1997, Staden et al. 1998, Metz-Lutz et al. 1999, Baglietto et al. 2001), as well as normalization of performance when children were in remission from BCECTS (D’Alessandro et al. 1995, Lindgren et al. 2004). These results suggest that cognitive difficulties would be present only in the active phase of epilepsy. Hommet et al. (2001) conducted a longitudinal study using standardized tests in adolescents and young adults who had presented BCECTS in childhood. They did not observe any cognitive disorders in this population compared to controls. Titomanlio et al. (2003) compared 16 children aged 10-16 years in remission from BCECTS versus control children using computerized tasks; patients made significantly more errors than controls on the double-choice reaction time task, which suggests the presence of difficulties in decision-making. Some subtle cognitive deficits could therefore persist over time despite normalization of clinical performance. It would be interesting to review the current study population when the children are in remission from the epilepsy.

Conclusion

BCECTS appears to interfere with high attention control demand tasks, i.e. tasks that require inhibitory processes or cognitive flexibility. Epilepsy-related variables, such as age-at-onset of seizures, duration of epilepsy, laterality of discharges and medication do not appear to have any impact on these functions. Children with BCECTS also present slowed reaction times and a large number of omission errors. Age-at-onset of seizures and/or medication could have a negative impact on slowness and on short-term retention capacities. Duration of epilepsy does not appear to interfere with the development of executive and attentional functions, but could influence spatial constructive capacities and non-verbal reasoning.

Results of this study suggest a specific profile in children with BCECTS, namely less efficient attention control processes. The use of experimental tasks would be a useful tool with which to study this hypothesis.

References


