Neurocognitive and psychological comorbidities in patients with self-limited centrotemporal spike epilepsy. A case-control study

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Introduction. Self-limited epilepsy with centrotemporal spikes (SeLECTS) is the most frequent self-limited focal epilepsy. This study aimed to assess the cognitive, behavioral, and other neuropsychological aspects of children with SeLECTS, and compare them with a control group.

Subjects and methods. A case-control study was carried out between January and May 2022. Patients with SeLECTS, aged between 6 and 18 years, and followed-up at our hospital were selected for inclusion in the study. For each case, two age-matched controls were opportunistically recruited. All the participants performed the EpiTrack Junior® test, and their parents filled out the Child Behavior Checklist (CBCL).

Results. Eighteen patients were included (mean age: 8.7 ± 1.7 years). At SeLECTS' diagnosis, 83% of cases had adequate psychomotor development, and 17% had a neurodevelopmental disorder. The EpiTrack-Junior® and the Total Problems CBCL scores were not influenced by the laterality of the epileptic focus nor by the number of seizures. 61% of cases showed mild or significant impairment in the EpiTrack-Junior® test versus 44% of controls (p = 0.712), and 39% of cases vs. 14% of controls had 'clinically significant' scores on the Total Problems CBCL scale (p = 0.087).

Conclusions. Although this study did not find statistically significant differences between cases and controls, it should be noted that most patients with SeLECTS had a mild or significant disability in executive functions. A considerable percentage of cases were in the pathological range regarding emotional/behavioral problems. This study highlights the importance of screening the cognitive, behavioral, and emotional problems in all patients with SeLECTS.

Key words. Behavioral problems. Cognitive impairment. Epilepsy. Neuropsychological tests. Seizures. Self-limited epilepsy with centrotemporal spikes.

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Introduction

Self-limited epilepsy with centrotemporal spikes (SeLECTS) is a self-limited epilepsy syndrome, formerly known as benign rolandic epilepsy or benign epilepsy with centrotemporal spikes, which begins in children in their early school years [1].

SeLECTS is the most frequent self-limited focal epilepsy and accounts for approximately 6%-7% of all childhood epilepsies [2,3]. Its incidence is approximately 6.1 per 100,000 children aged <16 years per year [4,5].

While epilepsy is active, behavioral and neuropsychological deficits may rarely emerge or worsen, particularly in language and executive functioning [6,7].

Focal epilepsies with onset during childhood are often self-limited and usually of unknown cause [8,9]. These conditions have been referred to, in the past, as 'benign' or 'idiopathic'. The term 'benign' is no longer recommended, as it fails to acknowledge the comorbidities present in some individuals. Indeed, recent studies have demonstrated that children with SeLECTS are at a higher risk for cognitive, behavioral, or emotional difficulties in association with frontal lobe dysfunctions, with speech impairment and executive dysfunction being the most prominent [9-13]. Causes are multiple and may be influenced by several factors, including the epilepsy type, its etiology, age of onset, duration of the disease, presence of cortical structural changes, duration and severity of seizures, and adverse effects of antiepileptic therapy [12,13]. Studies suggest that before the first epileptic seizure, 50% of children have subtle cognitive deficits, agitation, inattention, and depressive symptoms, changes that remain even after seizures are controlled or remitted [10,13]. As such, even children with self-limited epilepsies are more likely to experience psychosocial problems in adolescence and adulthood, with a higher prevalence of psychiatric illness [14,15]. However, there is no clear delineation of a

uniform neurocognitive profile for children with SeLECTS. The main aim of the present study was to assess the cognitive, behavioral, and other neuropsychological aspects in children with SeLECTS (cases). Our secondary aim was to compare the profiles of cases with those of a control group without known neurological disorders.

Subjects and methods

Cases and controls

This case-control study assessed children diagnosed with SeLECTS and pediatric medical follow-up at our hospital center between April 2019 and April 2022. Children with the referred follow-up appointments were eligible for inclusion if they were between ages 6 and 18, had SeLECTS (in accordance with International League against Epilepsy diagnostic criteria), were able to read aloud the numbers 1 and 2, and to count from 1 to 20. For each case, two age-matched control participants were identified. Control subjects were randomly recruited from children who had general pediatric follow-up at the same medical center. Children were included as controls if they had no personal history of epilepsy or another neurological disease, no known formal diagnosis of neurodevelopmental disorders, and were matched to cases for age.

Measures and variables

Cases, controls, and their parents were asked to participate in the study before or after a medical appointment. If they accepted, parents of both cases and controls were asked to complete the Child Behavior Checklist (CBCL). At the same time, one of the research team members administered the EpiTrack-Junior® test to the child.

The CBCL is a questionnaire completed by parents and one of the three components of the Achenbach System of Empirically Based Assessment (ASEBA). The ASEBA is used to screen behavioral and emotional problems in children and adolescents. The CBCL consists of 113 questions, scored on a three-point Likert scale (0 = absent; 1 = occurs sometimes; and 2 = occurs often), and the time frame for item responses is the past six months. The 2001 revision of the CBCL, the CBCL/6-18 (used with children from 6 to 18 years old), is made up of eight syndrome scales: anxious/depressed; withdrawn/depressed; somatic complaints; social problems; thought problems; attention problems; rule-breaking behavior; and aggressive behavior. These group into two higher-order factors: internalizing and externalizing. Regarding the Total Problems score, scores <60 are the normal range, 60-63 represent borderline scores, and scores >63 represent the clinical range. The ASEBA components are valid and reliable assessment tools, including their Portuguese version [16,17].

EpiTrack-Junior® was developed as a 12 to 15-minute test (ages from 6 to 18) with six tasks addressing attention, executive functions, and working memory: interference; connecting numbers; connecting numbers and circles; maze test; word fluency; and inverted digit span.

EpiTrack-Junior® total score ranges from 6 to 56 points. Scoring followed the available test protocol for Portugal, where categorization may differ slightly from the cutoff scores published in the original article. Our participants' performance was divided into four categories: good (≥36 points), average (31-35 points), mild impairment (29-30 points), and significant impairment (≤28 points). Several studies have revealed that the pediatric version of EpiTrack® is a valid and reliable screening tool for assessing attention and executive functions in children and adolescents. It is a tool widely used in clinical practice in children and adolescents with epilepsy, for example, to assess the side effects of antiepileptic drugs, but also in the context of scientific research, including in the comparison between children with and without epilepsy [18-20]. Our research group obtained formal authorization from Eisai, which acquired the rights to distribute the test in 2019, to use this tool in its European Portuguese version.

Assessments occurred between January 2022 and May 2022 in two settings in our hospital center: Child and Adolescent Psychiatry Service (cases) and Pediatrics Service (controls). For this study, information on SeLECTS diagnosis-related variables was retrieved from hospital charts for children who consented and completed the assessment.

Ethical approval was obtained from the institutional review board. All participants and one of their parents signed informed consent forms before enrollment.

Statistical analysis

Statistical analyses were performed with IBM SPSS® Statistics, version 22. A p value less than 0.05 ($p < 0.05$) was considered statistically significant.

Continuous variables were summarized as mean and standard deviation or as the median and inter-

quartile range (IQR), according to the normal or non-normal data distribution, and compared using parametric tests (Student's *t* test and one-way ANOVA) and non-parametric tests (Mann-Whitney U test and Kruskal-Wallis test), respectively. The categorical variables were described as frequencies and percentages and compared using the χ^2 test.

Results

Eighteen patients with SeLECTS, seven (39%) females and 11 (61%) males, fulfilled the inclusion criteria and agreed to participate in the study. Thirty-six controls, 21 (58%) females and 15 (42%) males, were randomly recruited from pediatric appointments and included in the study.

On the date of the study assessment, the youngest patient was 6 years old, and the oldest was 11 years (mean age 8.7 ± 1.7 years). The mean age at diagnosis of epilepsy was 7.3 ± 1.5 years, and the mean duration of epilepsy was 18.3 ± 10.9 months (Table I).

Only three patients had febrile seizures in childhood, and only four had a family history of epilepsy. At SeLECTS' diagnosis, 15 (83%) patients had adequate psychomotor development, and three (17%) children had a previously diagnosed neurodevelopmental disorder, namely intellectual developmental disorder, attention deficit hyperactivity disorder, and developmental language disorder.

Thirteen cases underwent cerebral magnetic resonance imaging, which was normal in 11 patients, one child had a parahippocampal cyst, and another had a Chiari malformation type I.

Regarding the lateralization on the electroencephalogram at diagnosis, nine patients had left centrotemporal spikes, five had right centrotemporal spikes, and four had bilateral. None of the patients showed continuous spike-waves during sleep on the electroencephalogram. When comparing patients according to the centrotemporal spikes lateralization on the electroencephalogram (left, right or bilateral), we did not find a statistically significant difference in the EpiTrack-Junior® score or the Total Problems CBCL score (p = 0.186 and 0.253, respectively).

By the time of the study, 67% of patients had experienced only one or two clinical seizures. The number of seizures (<3 or ≥3 seizures) did not influence the performance on EpiTrack-Junior® (p = 0,218) or the Total Problems CBCL score (p = 0,606). In the present study, the duration of disease (<1 or ≥1 year) did not affect EpiTrack-Junior® or the Total Problems CBCL score (p = 0,754 and 0,430, respectively).

Table I. Demographic and clinical characteristics of the cases.

	Cases (n = 18)
Sex	
Female	7 (39%)
Male	11 (61%)
Age (years), mean ± SD	8.7 ± 1.7
Age (years) at diagnosis, mean ± SD	7.3 ± 1.5
Duration of epilepsy (months), mean ± SD	18.3 ± 10.9
History of febrile seizures	3 (17%)
Family history of epilepsy	4 (22%)
Psychomotor development at diagnosis	
Adequate	15 (83%)
Neurodevelopmental disorder	3 (17%)
Lateralization on EEG at diagnosis	
Left	9 (50%)
Right	5 (28%)
Bilateral	4 (22%)
Number of seizures	
≤2	12 (67%)
≥3	6 (33%)
Cerebral MRI Findings (n = 13)	
Normal	11 (61%)
Parahippocampal cyst	1 (6%)
Chiari malformation type I	1 (6%)
Antiepileptic drugs	
None	10 (56%)
Monotherapy	8 (44%)

EEG: electroencephalogram; MRI: magnetic resonance imaging; SD: standard deviation.

Ten patients were not taking medications, and eight were treated with an antiepileptic drug in monotherapy –levetiracetam (n = 2) and valproic acid (n = 6)–. We did not observe a significant difference in the EpiTrack-Junior® score (p = 0.417) and the Total Problems CBCL score (p = 0.315) between non-treated patients and those treated with an antiepileptic drug.

Regarding executive functions (Table II), 11 (61%) patients showed impaired performance in EpiTrack-Junior®, including children both with

Table II. Comparison of EpiTrack Junior® and CBCL results between cases and controls.

	Cases (*n* = 18)	Controls (*n* = 36)	*p* value
EpiTrack Junior® Score, mean ± SD	29.8 ± 4,6	31.0 ± 4.1	0.314
EpiTrack Junior® performance categories			
Good	2 (11%)	5 (14%)	0.712
Average	5 (28%)	15 (42%)	
Mildly impaired	6 (33%)	9 (25%)	
Significantly impaired	5 (28%)	7 (19%)	
Total Problems CBCL score, median (IQR)	26.5 (55)	23.0 (26)	0.165
Total Problems CBCL score			
Normal	10 (55%)	25 (69%)	0.087
Borderline	1 (6%)	6 (17%)	
Clinical	7 (39%)	5 (14%)	
Internalizing problems CBCL score, median (IQR)	12.0 (16)	9.0 (11)	0.201
Externalizing problems CBCL score, median (IQR)	6.0 (17)	5.5 (5)	0.45

CBCL: Child Behavior Checklist; SD: standard deviation; IQR: interquartile range.

mild and significant impairment, versus 16 (44%) controls (p = 0.712). The mean EpiTrack-Junior® score was 29.8 ± 4.6 in the patients' group and 31.0 ± 4.1 in the control group (p = 0.314).

The analysis of the CBCL showed that 7 (39%) patients versus five (14%) controls had 'clinically significant' scores on the Total Problems CBCL score (p = 0.087). The median Total Problems CBCL score was 26.5 (IQR: 55) in the patients' group and 23 (IQR: 26) in the control group (p = 0.165). Regarding the CBCL scores for internalizing and externalizing problems, the patients' medians were 12 (IQR: 16) and 6 (IQR: 17), and the controls' medians were 9 (IQR: 11) and 5.5 (IQR: 5) (p = 0.201 and 0.450, respectively).

Discussion

Previous studies have shown that, although patients with SeLECTS usually have a full-scale intelligence quotient in the average range, they may have cognitive impairments, learning difficulties, and behavioral problems [6,21,22].

In our study, we did not find statistically significant differences between the group of cases and controls in the performance of the EpiTrack-Junior®, which assesses attention, executive functions, and working memory. However, we consider it is relevant to note that the Epitrack Junior® score mean was lower in the patients' group (29.8 ± 4.6 versus 31.0 ± 4.1), and most patients (61%) had mild or significant impairment versus 44% of controls. The lack of statistical significance may be due to the small sample size and some patients' short course of the disease.

Our results did not reveal differences between patients with epilepsy diagnosed less than one year ago and those with more prolonged epilepsy. However, the implication of the duration of epilepsy on cognitive and behavioral outcomes is still not fully understood [22]. Consequently, it will be essential to repeat these assessments to understand the evolution over time.

This study verified that the EpiTrack-Junior® score and the Total Problems CBCL score were not significantly influenced by the laterality of the epileptic focus nor by the number of seizures. These results are in agreement with other published studies [6].

According to scientific evidence, the occurrence of centrotemporal spikes (with or without seizures), especially at a young age (below 6 years) and for an extended period, is the most meaningful contributor to language, cognitive, and behavioral deficits in SeLECTS. While the distribution of centrotemporal spikes (left, right, bilateral) seems to have little significance [13].

Several studies have reported elevated rates of behavior problems and affective disturbance, including deficits in the ability to recognize and express interpersonal relations, aggressive behavior, attention problems, and anxiety/depression, in children with SeLECTS compared to healthy controls [21-24]. Özgen et al concluded that behavioral disorders may be present in approximately one-third of patients with SeLECTS and that early onset of seizures and the presence of bilateral interictal epileptic discharges may be risk factors for symptoms of behavioral problems in children with SeLECTS [25]. In our study, CBCL median results were in the borderline/clinical range for 45% of cases and 31% of controls. While those differences were not statistically significant, it is worth mentioning that almost half of the cases were in the pathological/'impaired' range according to their parents' perception.

Samaitienė et al demonstrated that children with SeLECTS had more aggressive behavior, social problems, attention problems, and anxiety/depression than controls. However, these findings were only significant in a group of patients treated with antiepileptic drugs and with an average duration of epilepsy of over two years [21,26].

Pathophysiological mechanisms responsible for cognitive and neuropsychological deficits are still unclear [22]. Some studies support the hypothesis that cognitive and behavioral impairments in SeLECTS are not the result of clinical seizures but are related to the pathological interictal electrical activity or a specific synaptic reorganization due to frequent electrical discharges [6,27]. Recent studies using diffusion tensor imaging examinations have shown widespread gray matter changes in SeLECTS, and others, using functional magnetic resonance imaging, found functional changes involving cerebral networks [22]. Therefore, there is evidence that SeLECTS has an impact on structural and functional brain development. However, whether these structural and functional changes are an underlying part of the syndrome or a consequence is not entirely clear [21].

Our study has the strengths of having an aged-matched control group and using validated tools to assess executive functions and screen behavioral and emotional problems. However, it has some limitations, such as small sample size and including patients with and without antiepileptic treatment. There is evidence that some antiepileptics drugs can negatively affect cognition, making it challenging to differentiate between disease and drug contribution to the development of cognitive impairment [6]. However, in our sample of cases, we did not find significant differences in the results obtained by patients under antiepileptic treatment and patients without drugs. From a behavioral and emotional perspective, having other informants (for example, teachers) could be interesting.

Conclusion

This study highlights the importance of screening the cognitive, behavioral, and emotional problems in all patients with SeLECTS. Using validated neuropsychological tests allows timely and adequate diagnosis and management of the comorbidities.

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Comorbilidades neurocognitivas y psicológicas en pacientes con epilepsia de la infancia con puntas centrotemporales. Un estudio de casos y controles

Introducción. La epilepsia de la infancia con puntas centrotemporales (EIPCT) es la epilepsia focal autolimitada más frecuente. Este estudio tenía como objetivo evaluar los aspectos cognitivos, conductuales y otros aspectos neuropsicológicos de niños con EIPCT, y compararlos con un grupo de control.

Sujetos y métodos. Se realizó un estudio de casos y controles entre enero y mayo de 2022. Se seleccionó para su inclusión en el estudio a pacientes con EIPCT, con edades comprendidas entre 6 y 18 años, en seguimiento en nuestro hospital. Por cada caso, se reclutó, de forma aleatoria, a dos controles de la misma edad. Todos los participantes realizaron la prueba EpiTrack Junior®, y sus padres rellenaron la lista de verificación del comportamiento infantil (CBCL).

Resultados. Se incluyó a 18 pacientes (edad media: 8,7 ± 1,7 años). En el momento del diagnóstico de EIPCT, el 83% de los casos presentaba un desarrollo psicomotor adecuado, y el 17%, un trastorno del neurodesarrollo. Las puntuaciones del EpiTrack-Junior® y de la escala total de problemas de la CBCL no se vieron influidas por la lateralidad del foco epiléptico ni por el número de crisis. El 61% de los casos mostró un trastorno leve o significativo en la prueba EpiTrack-Junior® frente al 44% de los controles (p = 0,712), y el 39% de los casos frente al 14% de los controles tuvieron puntuaciones 'clínicamente significativas' en la escala total de problemas de la CBCL.

Conclusiones. Aunque este estudio no encontró diferencias estadísticamente significativas entre casos y controles, cabe señalar que la mayor parte de los pacientes con EIPCT presentaba un deterioro leve o significativo en las funciones ejecutivas. Un porcentaje considerable de casos se encontraba en el rango patológico en cuanto a problemas emocionales/conductuales. Este estudio destaca la importancia de examinar los problemas cognitivos, conductuales y emocionales de los pacientes con EIPCT.

Palabras clave. Crisis epilépticas. Deterioro cognitivo. Epilepsia. Epilepsia de la infancia con puntas centrotemporales. Problemas de conducta. Pruebas neuropsicológicas.