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Cognitive profile in BECTS treated with levetiracetam: A 2-year follow-up

Francesca Felicia Operto [a,*], Grazia Maria Giovanna Pastorino [a,d], Roberta Mazza [b], Michele Roccella [c], Marco Carotenuto [d], Lucia Margari [b], Alberto Verrotti [e]

[a] Child Neuropsychiatry Unit, Department of Medicine, Surgery and Dentistry, University of Salerno, Salerno, Italy
[b] Child Neuropsychiatry Unit, Department of Basic Medical Sciences, Neuroscience and Sense Organs, University of Bari "Aldo Moro", Bari, Italy
[c] Department of Psychological, Pedagogical and Educational Sciences, University of Palermo, Palermo, Italy
[d] Department of Mental Health, Physical and Preventive Medicine, Clinic of Child and Adolescent Neuropsychiatry, Università degli Studi della Campania "Luigi Vanvitelli", Naples, Italy
[e] Department of Pediatrics, University of L'Aquila, L'Aquila, Italy

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ABSTRACT

Introduction: Benign epilepsy with centrotemporal spikes (BECTS) is a common epileptic syndrome in childhood, characterized by brief and infrequent partial motor seizures, with or without generalization and mostly recurring during sleep. Because of its favorable efficacy, tolerability, and safety profile, levetiracetam (LEV) monotherapy is often administered in these patients. Long-term effects of LEV therapy and its influence on cognitive functions remain controversial.
Purpose: This evaluated the changes in the cognitive profile of children with BECTS treated with LEV monotherapy for 2 years, compared with a control group of children with specific learning disabilities.
Method: Our patient cohort included 20 children aged 8–14 years diagnosed as having BECTS and administered LEV monotherapy and 10 age/sex-matched controls with specific learning disabilities. All participants underwent a standardized test for assessing cognitive profile (Wechsler Intelligence Scale for Children – Fourth Edition [WISC-IV]) before drug therapy and after 2 years of treatment. Average LEV blood level and electroencephalographic (EEG) recordings were periodically monitored. Several factors such as age, sex, response to therapy, and EEG pattern changes were considered. Statistical analysis was performed using Student's *t*-test for paired and independent samples. $p < 0.05$ was considered statistically significant.
Results: Children administered LEV for 24 months showed a mild but statistically significant improvement in overall cognitive abilities. Verbal skills, visual–perceptual reasoning, working memory, and processing speed showed slight but significant improvement. In the control group, cognitive profile remained substantially unchanged at 2-year follow-up.
Conclusions: Not only do our data suggest a nonworsening of the cognitive profile in BECTS with LEV but, on the contrary, cognitive scores also improved over time, unlike the control group.

1. Introduction

Benign epilepsy with centrotemporal spikes (BECTS) is a neurological disorder that affects about 1–2% of school-age and preschool children [1], with an incidence of 6.2–21 out of 100,000 children under 15 years old [2]. Benign epilepsy with centrotemporal spikes is characterized by short-term focal onset aware seizures, which usually begin between 3 and 13 years of age and nearly always disappear by age 15–17. Most seizures occur from sleep, and some of them may evolve into generalized tonic–clonic seizures [3]. The electroencephalography (EEG) typically displays "blunt high-voltage centrotemporal spikes (CTS), often followed by slow waves that are activated by sleep and tend to spread or shift from side to side" [3]. Traditionally, it is believed that this condition has a relatively benign course, regardless of the frequency of seizures [4]. Nevertheless, an ever-increasing literature has shown that children with BECTS perform worse than their peers in some cognitive and behavioral tasks [5], especially in some specific cognitive domains such as language and verbal memory [6,7]. It is still unclear whether these changes are originally part of the syndrome or a consequence of the seizures or EEG abnormalities [5].

The appropriate time at which drug therapy should be initiated in patients with BECTS is still under debate. An international consensus has not yet been reached; henceforth, this decision still depends on the clinician's judgment. The introduction of antiepileptic medication (antiseizure drug [ASD]) is generally necessary in the case of frequent,

Abbreviations: ASD, antiseizure drug; BECTS, benign epilepsy with centrotemporal spikes; CTS, centrotemporal spikes; LEV, levetiracetam; PRI, Perceptual Reasoning Index; PSI, Processing Speed Index; SLD, specific learning disorders; TIQ, Total Intelligence Quotient; VUI, Verbal Understanding Index; WISC-IV, Wechsler Intelligence Scale for Children – Fourth Edition; WMI, Work Memory Index.

* Corresponding author.
E-mail address: opertofrancesca@gmail.com (F.F. Operto).

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intense seizures that occur in wakefulness or are a source of concern for patients and their parents [8,9]. Furthermore, if the above-mentioned cognitive difficulties are caused by CTS and/or seizures, there is potential for intervention with antiepileptic medications [5]. However, some ASDs may worsen cognitive problems; certain drugs such as topiramate and valproic acid, especially in polytherapy, have been associated with cognitive and behavioral adverse effects [10]. Given its favorable pharmacokinetic profile [11,12] and good tolerability and safety [13–17], levetiracetam (LEV) was considered a viable alternative in monotherapy in pediatric patients with epilepsy [18].

This drug acts through a peculiar mechanism of action —in comparison with the other ASDs— as it binds to the SV2A synaptic vesicle protein, regulating the mechanisms of exocytosis necessary for neurotransmitter release [19]. Levetiracetam showed good broad-spectrum antiepileptic efficacy in both focal and generalized epilepsy [15,16], with modest adverse effects. Among the main undesirable effects are drowsiness, asthenia, dizziness, irritability, nervousness, and aggression [20,21]; behavioral effects appear to occur more frequently in younger patients (under 4 years of age). They have usually early onset, even during the titration phase, and in many cases, at low dosage (<20 mg/kg/day); however, they are always reversible after discontinuation of therapy [22]. Levetiracetam showed a good efficacy in reducing the frequency of seizures and CTS in boys with BECTS [23–27]. Moreover, with regard to the cognitive profile, LEV alone has not been described as having negative cognitive effects [28,29]; on the contrary, in some cases, the use of this drug seems to be related to an improvement of executive functions and verbal skills [30]. In literature, however, there are still few studies that evaluate cognitive effects through standardized tests in children, and these studies often stop in the short term [31]. The aim of our observational, retrospective, monocentric study was to evaluate changes in the cognitive profile in boys and adolescents with BECTS in monotherapy with LEV through a 24-month monitoring.

2. Material and methods

2.1. Sample selection

Twenty patients aged between 8 and 14 with a diagnosis as having BECTS were recruited retrospectively at the Child Neuropsychiatry Unit of the University Hospital of Salerno. The diagnosis was established on the basis of the typical clinical semiology of seizures and the EEG findings of CTS.

All patients who met the following eligibility criteria were included in the study: Total Intelligence Quotient (TIQ) in the normal range (TIQ ≥ 70) measured by the Wechsler Intelligence Scale for Children–Fourth Edition (WISC-IV) [32], diagnosis of BECTS, LEV monotherapy for 24 months, and good control (>75% reduction) of the seizures after the introduction of drug therapy.

All patients presenting other forms of epilepsy were excluded from the study, including atypical forms of BECTS, epileptic encephalopathy with continuous spikes and waves during sleep, and Landau–Kleffner syndrome. Even subjects with neurological (cerebral palsy, intellectual disability, neurodegenerative diseases, or migraine), psychiatric, or other relevant medical conditions (endocrinopathies, metabolic, hepatic, cardiac, or renal disorders) were excluded from the study. All recruited patients underwent LEV therapy, reaching the therapeutic dose within 1–2 weeks. The dose has been established individually, aiming to achieve good seizure control and good tolerability. Once the therapeutic dose was reached, there were no further additions of LEV or other ASDs. Serum levels of LEV and EEG have been periodically monitored, in the context of the typical follow-up meetings. All participants were also administered the WISC-IV standardized test by a single child neuropsychiatrist, so as to evaluate the cognitive profile at time 0 (before starting the therapy with LEV) and at time 1 (after 2 years of treatment).

A control group was also recruited, including 10 patients who attend the same hospital unit for specific learning disorders (SLD). Inclusion criteria were the standard cognitive level (TIQ ≥ 70 to WISC-IV) and the diagnosis of SLD. Exclusion criteria were the presence of neurological, psychiatric, or other general medical pathologies that could interfere with the cognitive performances. In all patients of the control group, the diagnosis of epilepsy was excluded, and all had a normal EEG finding. Furthermore, the control group underwent the same standardized WISC-IV psychometric test at the time of diagnosis and after 2 years, as part of the normal diagnostic and follow-up evaluations. To guarantee the homogeneity of the two groups, the variables age, sex, intellectual level, and level of maternal education were taken into consideration.

2.2. Wechsler Intelligence Scale for Children – Fourth Edition (WISC-IV)

To evaluate the intellectual profile of our patients, we chose to use the WISC-IV battery, a standardized test for children and teenagers from 6 to 16 years. It consists of 10 subscales through which it is possible to calculate the following indices:

- Verbal Understanding Index (VUI): language and verbal skills.
- Perceptual Reasoning Index (PRI): nonverbal and fluid reasoning.
- Work Memory Index (WMI): auditory attention and working memory.
- Processing Speed Index (PSI): selective attention, speed of visual information processing.
- TIQ: general cognitive profile.

2.3. Statistical analysis

All clinical variables were subjected to statistical analysis. The raw scores obtained from the WISC-IV were converted into weighted scores to be compared to a standard reference population. The standard range

Table 1
Clinical characteristics of the levetiracetam group and the control group.

	BECTS	SLD	p-Value
Mean age (years)	10.3 ± 1.78	11 ± 1.4	0.289
Sex	15/20 male	5/10 male	0.231
Maternal education level	15/20 high school 5/20 university	9/10 high school 1/10 university	0.633
Seizures' frequency	12/20 weekly 8/20 monthly	–	–
Therapeutic dosage of LEV	Minimum = 500 mg/day Maximum = 1750 mg/day Mean = 1037.5 ± 399.6 mg/day	–	–
Response to therapy	20/20 seizures-free	–	–
Adverse effects	1/20 dizziness; 2/20 headache; 1/20 irritability		
Total Intelligence Quotient (time 0)	102.30 ± 7.87	101.50 ± 9.58	0.809

BECTS, benign epilepsy with centrotemporal spikes; SLD, specific learning disorder.

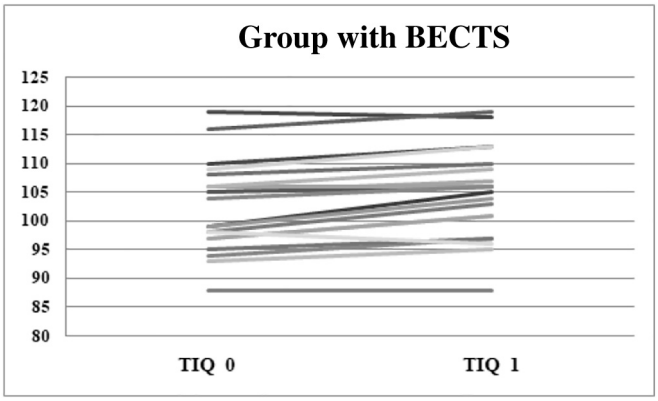

Fig. 1. Total Intelligence Quotient (TIQ) scores in the group with BECTS at time 0 and time 1.

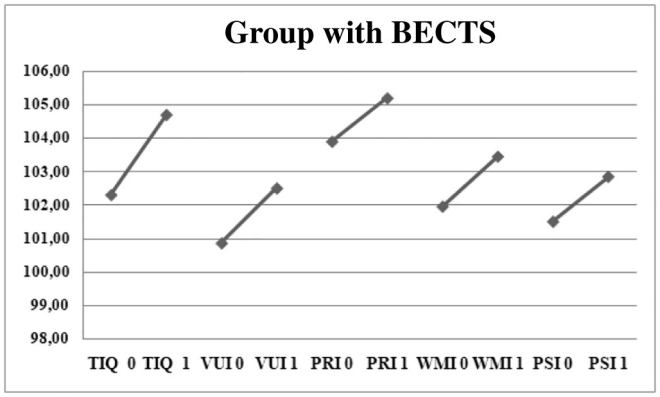

Fig. 2. Comparison between the mean scores at time 1 versus time 0 in the group with BECTS. TIQ = Total Intelligence Quotient. VUI = Verbal Understanding Index. PRI = Perceptual Reasoning Index. WMI = Work Memory Index. PSI = Processing Speed Index.

of each scale includes weighted scores >70 (mean = 100 ± 15). The results of the WISC-IV test were expressed as mean and standard deviation. To assess the significant differences between the mean scores of the two groups, the two-tailed Student's *t*-test for independent samples was used. A two-tailed Spearman's correlation was used to evaluate the correlation between WISC-IV scores, daily dose of LEV, and average serum levels of LEV. The analysis of variance (ANOVA) test was used to analyze the differences among the two groups regarding parameters such as sex, age, and maternal education. The Statistical Package for Social Science (SPSS) - version 23.0 (IBM Corp. 2015) program was used for statistical analysis. A value of $p < 0.05$ was considered statistically significant.

2.4. Ethics

All patients and their parents were provided a clear and detailed explanation about the purposes of the study and the procedures involved. Parents of patients provided their informed consent in written form. The procedure was approved by the local ethics committee, according to the rules of good clinical practice, in keeping with the Declaration of Helsinki.

3. Results

3.1. Participants

Our patient cohort is composed of 20 children, aged 8–14 (mean = 10.3 ± 1.78) years diagnosed as having BECTS, and 10 controls aged 8–14 (mean = 11 ± 1.4) years with a previous diagnosis of as having SLD.

Table 1 summarizes the clinical characteristics of the LEV group and the control group.

Mean LEV serum levels measured after 8, 18, and 24 months were 9.6, 9.6, and 9.0 μg/mL, respectively. In 7 of 20 patients, an improvement in the EEG trace was observed, while in the other ones, the EEG remained substantially unchanged.

Statistical analysis revealed no significant difference between the two groups regarding age ($p = 0.289$), sex ($p = 0.231$), and level of maternal education ($p = 0.633$). No statistically significant difference was found between the TIQ in the two groups measured at time 0 ($p = 0.809$).

3.2. Longitudinal comparison: time 1 vs time 0

At time 0, all patients diagnosed as having BECTS had a cognitive profile in the standard, with scores of TIQ > 70 (Fig. 1). Individual TIQ scores were not related to seizure frequency ($p = 0.693$). Also, the scores related to the other WISC-IV indices all fell into the norm.

From the comparison between the mean scores at time 1 versus time 0 in the study group – i.e., after 2 years of treatment as monotherapy with LEV, a statistically significant improvement of the TIQ and of all the other indexes emerged (Table 2, Fig. 2). The individual TIQ scores were not related to the assumed LEV dose ($p = 0.439$) or to the average LEV serum concentration ($p = 0.348$).

Regarding the control group, at time 0, the TIQ values (Fig. 3) and all the subindices of the WISC-IV were within the standard range. Two years later (time 1), the average TIQ remained substantially unchanged. From the comparison of the average scores of the other indexes, no statistically significant difference emerged (Table 2, Fig. 4).

4. Discussion and conclusions

The aim of our study was to monitor cognitive functions in children and adolescents diagnosed as having BECTS who were assuming LEV for 2 years and compare them with a group of children with SLD.

The data analysis revealed a significant improvement in the overall cognitive profile (Total Intelligence), as well as in the verbal understanding, perceptual reasoning, work memory, and processing speed in patients whose seizures are treated with LEV, while in the control group, all these remains substantially unchanged. The presence of the

Table 2
p-Value of comparison between the mean scores at time 1 versus time 0 in both groups.

	BECTS			SLD		
	Time 0	Time 1	p-Value	Time 0	Time 1	p-Value
TIQ	102.30 ± 7.87	104.70 ± 7.86	**0.0001**	101.50 ± 9.58	99.50 ± 5.97	0.5586
VCI	100.85 ± 8.59	102.50 ± 8.28	**0.0358**	109.20 ± 15.89	108.40 ± 11.54	0.7937
PRI	103.90 ± 8.57	105.20 ± 8.67	**0.0469**	109.20 ± 8.31	107.80 ± 12.86	0.7362
WMI	101.95 ± 7.86	103.45 ± 6.69	**0.0467**	89.80 ± 8.27	86.50 ± 12.02	0.4146
PSI	101.50 ± 7.94	102.85 ± 7.25	**0.0351**	86.50 ± 7.78	88.40 ± 7.97	0.4892

TIQ, full-scale Total Intelligence Quotient; VCI, Verbal Comprehension Index; PRI, Perceptual Reasoning Index; WMI, Working Memory Index; PSI, Processing Speed Index.
p-values > 0.05 are in bold.

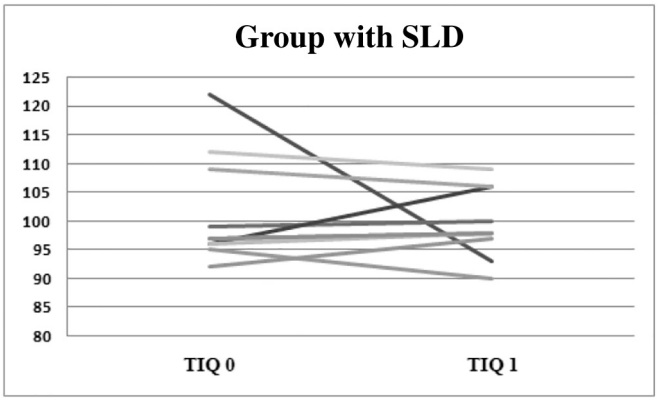

Fig. 3. Total Intelligence Quotient (TIQ) scores in the control group at time 0 and time 1. SLD = specific learning disorder.

control group allows us to exclude the influence of certain demographic and sociocultural factors on the results (age, sex, sociocultural level).

These results are consistent with a previous study [33,34]: a randomized, controlled study by Levisohn and colleagues, in 2009, showed that after 12 weeks of follow-up, there were no significant differences in cognitive parameters measured by the Leiter-R test in children with focal epilepsy who had taken LEV as add-ons (46 cases) or a placebo (27 cases) [35]. More recently, an open-label add-on study showed a stable cognitive profile in 103 children between 4 and 16 years who had been administered LEV for 48 weeks [36].

A more detailed analysis of the individual subindexes of the WISC-IV also revealed that verbal skills – expressed through the VUI index – were improved in our sample. These results are in agreement with those of a study by Piazzini et al., in 2007 [37]. The authors pointed to an improvement in verbal fluency skills in patients taking LEV, assuming a potential role of piracetam derivatives on the metabolism of cortical areas responsible for attention and language. Furthermore, performances involving the executive functions (working memory, selective attention, and processing speed), expressed by the WMI and PSI indexes, were improved in our patients. These results confirm and enrich those results that have already been highlighted in previous studies on adult populations [38,39].

A 2012 study by Cho et al. showed that the improvement of the cognitive profile following the introduction of LEV was related to the EEG changes typically induced by the drug (reduction of delta and theta bands, increase of the bands A2 and B2) in some specific cortical regions [40]. However, these data cannot be confirmed in our study because a spectral analysis of the EEG was not performed.

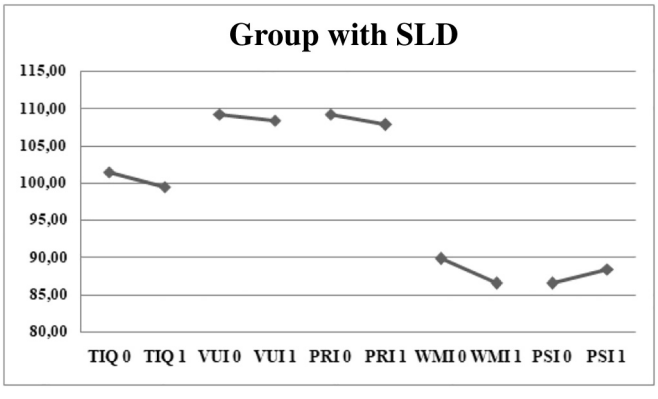

Fig. 4. Comparison between the mean scores at time 1 versus time 0 in the control group. TIQ = Total Intelligence Quotient. VUI = Verbal Understanding Index. PRI = Perceptual Reasoning Index. WMI = Work Memory Index. PSI = Processing Speed Index. SLD = specific learning disorder.

None of the recruited patients had significant adverse reactions over the 2 years of follow-up, with the exception of dizziness (1/20), headaches (2/20), and irritability (1/20), which are among the most common adverse effects of LEV [41] and have not requested, in any case, the suspension of treatment. This confirms the good tolerability profile of the drug.

Limitations of our study are the low sample size and the lack of a control group of subjects with BECTS treated with other ASDs or not pharmacologically treated. However, the 24-month follow-up is an important strength because there are no studies in the scientific literature that evaluate the cognitive profile through standardized tests in such for such a duration.

In conclusion, this study suggests that LEV does not negatively affect the cognitive profile of pediatric patients with BECTS, even in the medium to long term. Some cognitive skills could even improve, although these data need further verification. Therefore, considering that cognitive and executive functions are strictly related to school performance and adaptive and social skills, it may be useful to consider these factors when choosing ASD in order to improve quality of life, especially in the pediatric age group.

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Declaration of competing interest

The authors have no conflicts of interest relevant to this article to disclose.

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