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The influence of levetiracetam on psychosocial and behavioral functioning in children: A case–control and follow-up study

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ABSTRACT

Background: Levetiracetam, a widely used antiepileptic drug in children, has been associated with psychosocial and behavioral problems, which are also influenced by epilepsy variables, including duration or seizure frequency.
Purpose: The objective of this study is to investigate the frequency and timing of treatment-emergent psychosocial and behavioral problems in children receiving levetiracetam, irrespective of seizure variables which are possible confounders.
Methods: A prospective, case–control study with a 3-month follow-up was conducted. Consecutive children aged 6 to 16 years with new-onset partial seizures were included in case of starting treatment with either levetiracetam or valproic acid. Psychosocial and behavioral functioning were assessed using a set of standardized questionnaires including Strengths and Difficulties Questionnaire (SDQ) and Children's Depression Inventory (CDI) at baseline, 1 and 3-month follow-up. Patients' baseline scores were compared to healthy subjects. The difference in the follow-up SDQ and CDI scores was evaluated in patients receiving levetiracetam and valproic acid.
Results: A total of 101 participants were analyzed; 32 patients in levetiracetam group, 19 patients in valproic acid group and 50 healthy controls. Baseline SDQ and CDI scores were not statistically different between patients and healthy subjects ($p > 0.05$). No statistically significant difference was observed in CDI, total and subscale SDQ scores between patients receiving levetiracetam or valproic acid during the study period ($p > 0.05$). A girl aged 15 years receiving levetiracetam had a CDI score of 18 without suicidal ideation at baseline. She developed suicidal ideation and depression, which resolved after switching of levetiracetam to valproic acid, at the 1-month follow-up. No other psychiatric or behavioral side-effects were observed in other patients.
Conclusion: Psychosocial and behavioral side-effects of levetiracetam treatment are not frequent and they don't emerge in most of children at lower doses. At this dose, and after 3 months, using these specific instruments, we did not observe any difference between the valproic acid and levetiracetam treatment groups.

1. Introduction

Levetiracetam, a second-generation antiepileptic drug, has a broad spectrum of efficacy in focal and generalized epilepsies [1–3]. Its use in children is highly favorable due to the absence of pharmacokinetic interactions with other antiepileptic drugs, and relatively safe adverse event profile [4]. Clinical studies on safety demonstrated a tendency towards psychiatric and behavioral disturbances including depression, suicidal ideation, aggressiveness, affective disorder, emotional lability, and psychosis in patients receiving levetiracetam [5–14].

Patients with a history of behavioral disturbances, and children have been identified at greater risk for treatment-emergent behavior problems [14]. However, there are conflicting statements on the frequency, timing and associated clinical variables regarding the occurrence of behavioral problems in children receiving levetiracetam [5–14]. Epilepsy variables including duration, seizure type, severity, frequency and polytherapy are also the potential contributing factors on the neurobiological and psychosocial status which complicates interpretation of the direct relationship between levetiracetam and behavioral problems [15–17].

This prospective case–control study was conducted to investigate the frequency and timing regarding treatment-emergent psychosocial and behavioral problems in children receiving levetiracetam irrespective of seizure variables which are possible confounders.

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2. Materials and methods

2.1. Participants

Consecutive children aged 6 to 16 years with new-onset partial seizures, attending regular schools, were recruited from Pediatric Neurology Clinic at Istanbul Faculty of Medicine, between March 2016 and September 2016. Participants who were planned to start treatment with either levetiracetam or valproic acid according to the pediatric neurologists' decision were included in this prospective study. Patients with abnormal brain imaging findings, preexisting emotional and behavioral disturbances, family history of behavioral and psychiatric disorders, and accompanying chronic disease were excluded. The magnetic resonance imaging protocol included sagittal, axial, and coronal imaging planes at 1.5 T in all patients. Before starting antiepileptic drug, patients were screened for biochemical and metabolic parameters (including analysis of plasma lactate, creatine kinase, ammonia, amino acids, and urinary organic acids). There were 3 groups in this study; group 1, group 2 and group 3 consisted of patients on levetiracetam, patients on valproic acid, and healthy children, respectively. The control group matched for age, sex and socioeconomic status consisted of healthy children attending regular schools. Levetiracetam and valproic acid were administered at an initial dose of 10 mg/kg/day twice daily, and titrated up to 20 mg/kg/day by increments of 5 mg/kg/week. Complete blood count and biochemical parameters including plasma ammonia were analyzed at 1 and 3-month follow-up. Patients who had seizure after starting an antiepileptic drug were also excluded to avoid possible confounder effect of seizure recurrence.

The study protocol was approved by the Ethics Committees of the Istanbul Faculty of Medicine. All participants and/or their legal representatives signed a written informed consent.

2.2. Clinical data

Demographic informations of patients including age at seizure onset, epilepsy duration, number of seizures, and seizure frequency were recorded. The day before starting antiepileptic drug was taken as the baseline time point. Data on seizure frequency were recruited from daily diaries at baseline, 1- and 3-month follow-up visits. The seizure frequency was assessed as the number of seizures per month.

2.3. Psychosocial and behavioral functioning

Psychosocial and behavioral functioning were assessed using a set of standardized questionnaires at baseline, 1- and 3-month follow-up. Healthy control participants had the test for once that was examined for the presence of psychosocial and behavioral impairment. Standardized tests consisted of the Turkish version of Strengths and Difficulties Questionnaire (SDQ-Tur) filled out by parents and the Children's Depression Inventory (CDI) filled out by children [3,14,18]. The validity and reliability of SDQ and CDI were well-established in pediatric patients [19,20]. The SDQ is a structured questionnaire targeting emotional symptoms, conduct problems, hyperactivity and concentration difficulties, peer relationship problems and prosocial properties, comprising 25 items [3]. The CDI, a 27-item questionnaire, was administered to assess depressive symptoms, including suicidal ideation. The CDI total score ranges from 0 to 54 based on the sum of the scores for each item. The clinical depression was suspected when cut-off score of CDI was above 19 points or suicidal ideation was present. The used antiepileptic drug was planned to discontinue in case of serious behavioral disturbances, including suicidal ideation and depression. Patients with suicidal ideation were referred to an urgent psychiatric examination.

2.4. Statistical analysis

Quantitative variables were presented as means and standard deviations. The Shapiro–Wilk test was used to assess normality of demographic variables, and psychosocial and behavioral outcomes. Group differences in demographic variables and baseline psychosocial and behavioral outcomes which were not normally distributed were compared using Kruskal–Wallis test. A nonparametric Friedman test was used to compare psychosocial and behavioral outcomes for each group at baseline, 1-, and 3-month follow-up. $p < 0.05$ was accepted as statistically significant. All statistical analyses were performed using SPSS Statistics for Windows version 21.0 (IBM Corp., Armonk, NY, USA).

3. Results

3.1. Demographics

A total of 101 participants were analyzed; 32 patients in levetiracetam group, 19 patients in valproic acid group and 50 healthy controls. There was no significant difference in terms of age, sex, and socioeconomic status between 3 groups ($p = 0.41$). All participants were attending normal schools. Demographic and clinical characteristics of participants are listed in Table 1. All patients' biochemical and metabolic parameters were within normal range at baseline and during follow-up. The seizure frequency of the patients was less than two per month at baseline, and did not increase during follow-up. Antiepileptic medication was switched only in 1 patient due to psychiatric side-effect.

3.2. Neuropsychological and behavioral evaluation

All participants had the total CDI score of less than 19, and none had suicidal ideation at baseline. There was no statistically significant difference observed between the three groups in baseline CDI and total and subscale SDQ scores ($p > 0.1$, $p > 0.05$). There was no significant difference in CDI, total and subscale SDQ scores of group 1 between baseline and 1-month follow-up ($p > 0.05$). Suicidal ideation and depression emerged only in one girl (n = 32) aged 15 years in group 1. She had a CDI score of 18 without suicidal ideation at baseline, but she exhibited suicidal ideation at the 1-month follow-up. Also her CDI total score increased up to 40 accompanied by deterioration of SDQ score at 1-month follow-up. She was excluded from group 1 at 1-month after starting levetiracetam. A psychosocial stressor underlying depression was not detected in psychiatric examination. The emergence of depression was interpreted as levetiracetam side-effect which may resolve after discontinuation of the treatment. She was closely monitored for psychiatric symptoms without starting psychiatric medication. Levetiracetam was switched to valproic acid; suicidal ideation resolved, and CDI total score was regressed to 15 points within 1 month after starting valproic acid. SDQ total and subscale scores were also improved. She remained seizure-free during the follow-up. The frequency of treatment-emergent psychiatric side-effect was 3.1% in group 1. There was no significant difference observed between CDI,

Table 1
Demographic characteristics of participants.

	LEV group	VPA group	Healthy controls	*p*
n	32	19	50	
Sex, n (%)	15 F (46.9)	11 F (57.9)	26 F (52)	0.45
Age (years)				
Range	6–15	7–15	6–15	–
Mean	10.81	10.63	10.74	0.78
SD	2.74	2.56	2.65	
Mean number of seizures	2.06	2.10	–	0.58
Mean duration since first seizure (months)	3.9	3.68	–	0.46

Abbreviations: LEV = levetiracetam; F = female; SD = standard deviation; VPA = valproic acid.