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The Effect of Levetiracetam Therapy on Lipid Profile in Epileptic Children

Epileptik Çocuklarda Levetirasetam Tedavisinin Lipid Profili Üzerine Etkisi

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Abstract

Objective: The aim of this study was to evaluate the effect of levetiracetam (LEV) therapy on lipid metabolism in euthyroid nonobese epileptic children.

Methods: In this case-control study, we recruited 37 epileptic children receiving LEV monotherapy for at least 12 months and 54 healthy controls. Fasting blood samples were obtained for analyzing serum thyroid-stimulating hormone, free triiodothyronine (FT3), free thyroxine, total cholesterol (TC), high-density lipoprotein (HDL), low-density lipoprotein (LDL), triglycerides, Triglyceride/HDL ratio, and transaminases at the administration.

Results: There were nonsignificant elevated concentrations of TC HDL, LDL, aspartate aminotransferase (AST) and alanine aminotransferase in epileptic children with LEV monotherapy relative to healthy controls (p=0.32, p=0.29, p=0.80, p=0.27, and p=0.44 respectively). Although all subjects were euthyroid, serum level of FT3 was significantly elevated in individuals with epilepsy compared with healthy controls (p<0.001). Among prepubertal epileptic children receiving LEV monotherapy, LDL, TC, and AST levels were significantly higher compared to pubertal ones (p=0.02, p=0.03, and p=0.018 respectively).

Conclusion: Epileptic children who were treated with LEV monotherapy are susceptible to lipid metabolism alterations. Although they have the protective effect of elevated HDL from cardiovascular disease, they are also slightly at risk of dyslipidemia resulting from elevated LDL and TC. Therefore, close monitoring of individual risk groups like prepubertal children and male sex for dyslipidemia-associated diseases is mandatory.

Keywords: Child, epilepsy, levetiracetam, thyroid hormones, lipids

Öz

Amaç: Bu araştırmanın amacı, obez olmayan, ötiroid epileptik çocuklarda levetirasetam (LEV) tedavisinin lipid metabolizması üzerindeki etkisini değerlendirmektir.

Yöntem: Bu olgu-kontrol çalışmasına, en az 12 ay boyunca LEV monoterapisi alan 37 epileptik çocuk ile 54 sağlıklı kontrol alındı. Başvuruda serum tiroid uyarıcı hormon, serbest triiyodotironin (FT3), serbest tiroksin, toplam kolesterol (TC), yüksek yoğunluklu lipoprotein (HDL), düşük yoğunluklu lipoprotein (LDL), trigliseritler, trigliserit/HDL indeks ve transaminazların analizi için açlık kan örnekleri alındı.

Bulgular: Levetirasetam monoterapisi alan epileptik çocuklarda sağlıklı kontrollere kıyasla anlamlı olmayan yüksek total kolesterol, HDL, LDL, aspartat aminotransferaz (AST) ve alanin aminotransferaz (ALT) konsantrasyonları vardı (sırasıyla; p=0,32, p=0,29, p=0,80, p=0,27 ve p=0,44). Tüm denekler ötiroid olmasına rağmen, sağlıklı kontrollere kıyasla epileptik bireylerde serum FT3 düzeyi anlamlı olarak yüksekti (p<0,001). LEV monoterapisi alan prepubertal epileptik çocuklarda LDL, TC ve AST düzeyleri pubertal olanlara göre anlamlı derecede yüksekti (sırasıyla; p=0,02, p=0,03 ve p=0,018).

Sonuç: Levetirasetam monoterapisi alan epileptik çocuklar lipid metabolizması değişikliklerine duyarlıdır. Yüksek HDL'nin kardiyovasküler hastalıktan koruyucu etkisine sahip olmalarına rağmen, yüksek LDL ve TC'den kaynaklanan dislipidemi için de hafif risk altındadırlar. Bu nedenle, ergenlik öncesi çocuklar ve erkek cinsiyet gibi bireysel risk gruplarının dislipidemi ile ilişkili hastalıklar açısından yakından izlemi zorunludur.

Anahtar Kelimeler: Çocuk, epilepsi, levetirasetam, tiroid hormonları, lipitler

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Introduction

Epilepsy is one of the most common social health problems in children. The prevalence of epilepsy affects 0.8% of children in Turkey[1]. Conventional antiseizure medications are the first step of therapy for seizure control. Morbidity and mortality decreased by seizure control, whereas uncontrolled seizures increase the risk of cognitive and psychosocial decline in children[2,3]. However, admitting an antiseizure medication for a long time may cause an increased risk of drug-related comorbidities in some unpredicted ways at long-term follow-up.

Dyslipidemia is an abnormal serum composition of lipids and lipoproteins (LDL). Genetic and environmental factors caused dyslipidemia. Prior studies have demonstrated that antiseizure medications cause alterations in serum lipid levels[4-8]. In particular, total cholesterol (TC), low-density LDL, and total triglyceride (TG) levels were influenced both in children and adults treated with older antiepileptic drugs[9]. Decreased high-density lipoprotein (HDL) promoted by elevated TG and C-reactive protein (CRP) levels are associated with oxidative stress. McLaughlin et al.[10] showed that the TG/HDL ratio was a tool to identify dyslipidemia and insulin resistance. Hannon et al.[11] reported an association between the TG/HDL ratio and insulin resistance in obese children. Manco et al.[12] suggested that TG/HDL-C ratio is a useful screening tool to identify obese children at risk of impaired glucose tolerance. Quijada et al.[13] claimed that the TG/HDL ratio is a useful marker to identify children at risk of dyslipidemia, hypertension, and metabolic syndrome. Moreover, Yeom et al.[14] clarified that increased TG/HDL ratio in adolescence is associated with hypertension in early adulthood. Levetiracetam (LEV) is one of the most popular second-generation antiseizure drugs among pediatric neurologists. On reviewing the literature, several studies with pediatric patients have invested the safety profile and efficacy of LEV monotherapy in focal and generalized seizures found[15]. LEV is easily accessible and is estimated to be efficient as monotherapy, with a safe profile. The most suggested side effects of LEV therapy in children were behavioral side-effects such as aggression, hostility, and nervousness[16,17]. Several clinical studies regarding the lack of LEV's effect on thyroid status in children with epilepsy have been published previously[4-8]. The results of some studies between LEV treatment and lipid profile have been a controversial subject within the field[5,8,18-20]. Additionally, limited studies were conducted for examining the influence of LEV on lipid profile in pediatric epilepsy. There is an urgent need to address the safety problems about lipid profile alterations caused by LEV usage in pediatric epilepsy. One of the future comorbidities waiting for these children may be an elevated risk of cardiovascular diseases resulting from the alteration of their lipid profile.

To our knowledge, there is a lack of data about the lipid metabolism problems among epileptic children who are receiving LEV monotherapy. This study aimed to determine the effects of LEV on serum lipid parameters including TG/HDL ratio in euthyroid non-obese epileptic children.

Materials and Methods

In this single-center observational case-control study, we evaluated the children, were aged between 4 and 17 years who admitted to the pediatric neurology outpatient clinic from October 2020 to October 2021. The same pediatric neurologist and pediatric endocrinologist examined and defined the two groups as one study group (Group 1) and one control group (Group 2). The epileptic children (n=37) diagnosed with epilepsy with at least two focal seizures within a year, and treated with LEV monotherapy for at least 12 months were included in Group 1. These epileptic children were compared to healthy volunteers (n=54) who were without any neurological condition or chronic disorder or were not under any medication in Group 2.

Children with other medical conditions (neurological, endocrinological, genetic, etc.) that required continuous medication, or children with abnormal nutritional status (malnutrition, overweight or obese), or epileptic children who were receiving poly-therapy were excluded from the study.

The categorization of the seizure control of Group 1 was as follows: (a) "controlled" if the patient was free of seizures for more than one year, (b) "partially controlled" if the intervals of the seizures' were between seven to 30 days, and (c) "uncontrolled" if the seizures occurred within seven days or frequently occurred (>1/per day).

In Group 1, duration of illness (years), etiology of (structural, genetic, unknown), seizure type (focal onset, generalized onset, and unknown onset), type of epilepsy (focal, generalized, combined generalized-focal, and unknown epilepsy), the dosage of LEV (milligrams) were retrieved from patient's medical records. The seizure and epilepsy classification of Group 1 were categorized in terms of the recommendations of the International League Against Epilepsy, 2017[21].

The puberty stage was defined according to the Tanner scale by experienced pediatric endocrinologists. Subjects were categorized into prepubertal and pubertal stages. "Pubertal" boys were defined as having a testicular volume (testicular volume measured with a prader orchidometer) greater than 4 milliliters and "pubertal" girls were defined as having breast development at Tanner stage 2 (breast development with an elevation of breast and papilla; enlargement of the areola) and above[22]. The rest of the subjects were considered prepubertal by the Tanner scale correspondingly.

The medical records of the subjects were evaluated retrospectively using a standardized form; age (years), sex (male, female), length (centimeters), weight (kilograms), body mass index [(BMI), weight/length^2], pubertal status, laboratory tests [for thyroid-stimulating hormone (TSH), free triiodothyronine (FT3), free thyroxine (FT4), HDL, (LDL), triglycerides (TG), TC, aminotransferases (aspartate aminotransferase, alanine aminotransferase), uric acid, CRP] were noted retrospectively from patient records.

The thyroid status analyses were limited to age-dependent reference ranges for TSH (mIU/L), FT4 (pmol/L), and FT3 (pmol/L). For participants between the age of 4-11.9 years, the reference ranges were 0.2-3.0 mIU/L for TSH, 13.8-35.3 pmol/L for FT4, and 4.6-8.2 pmol/L for FT3. For participants older than 11.9 years, we used published thyroid hormone values by Campbell et al.[23] to determine thyroid status. The lipid profile was assessed in a morning blood sample after a 12-hour fast and the normal lipid values were evaluated according to the National Cholesterol Education Program guidelines[24]. For TG/HDL ratio, previous studies were guided, and values were obtained with the formula [fasting blood triglyceride value (mg/dL)/fasting blood HDL value (mg/dL)].

The informed consent form was obtained from parents of all the participants. The study was approved by the Balıkesir University Regional Ethics Committee (2021/186-08/09/21).

Statistical Analysis

All statistical analyses were performed using Statistical Package for Social Sciences software for Windows 25.0. Sample size was calculated by using online statistical sample size calculator (G*Power version 3). Compliance of quantitative data with normal distribution was investigated using Kolmogorov-Smirnov test and histogram graphics. Continuous variables were displayed using means ± standard deviation (SD). Categorical variables were compared using the chi-square test. If the distribution was homogeneous, Student's t-test was performed. If the variable did not have a normal distribution, the Mann-Whitney U test was performed. Differences were considered significant at $p<0.05$, coefficient interval 95%.

Results

Ninety-one children (patient: 37 and healthy control: 54) between the age of 4-17 years with a median age of 11.17 (4.4) years were included to the study. In total, 53.8% of the participants (n=49/91) were girls (male to female ratio 0.85:1). 48.6% of the Group 1 and 35.2% of Group 2 were pre-pubertal; 51.4% of Group 1 and 64.8% of Group 2 were pubertal. Table 1 presents the demographic data of the participants.

Table 1. Demographic characteristics and clinical data of the participants

	Group 1 n=37	**Group 2 n=54**	**p-value**
Age (years) mean ± SD	10.3±4.7	11.8±4.1	0.13[a]
Gender (n %)			
Male	18 (48.6)	24 (44.4)	0.69[b]
Female	19 (51.4)	30 (55.6)	
Weight (kg) mean ± SD	46.1±16.4	47.3±13.3	0.70[c]
Length (cm) mean ± SD	141±24.04	145±19.9	0.65[a]
BMI (kg/m^2) mean ± SD	22.4±2.8	22.04±2.3	0.78[a]
Puberty development scale (n %)			
Pre-pubertal	18 (48.6)	19 (35.2)	0.19[b]
Pubertal	19 (51.4)	35 (64.8)	

BMI: Body mass index, SD: Standard deviation, normally distributed data are presented as means ± standard deviation, non-normally distributed data are presented as median and interquartile ranges.

[a]: Non-normally distributed data were tested using the Mann-Whitney U test, [b]: x^2 test was used, [c]: Normally distributed data were tested using the Student's t-test. A $p<0.05$ was considered statistically significant

The mean age of group 1 (M/F =18/19) were 10.3 years. The duration of illness ranged from 1 to 5 years (mean ± SD: 1±1.08 years). In Group 1, the etiologies of patients were specified with the medical history, physical examination, laboratory tests, and neuroimaging. The etiology of 7 (18.9%) was structural, 17 (45.9%) genetic, and 13 (35.2%) with an unknown origin. The seizure types of 20 (54.1%) were focal onset, 15 (40.5%) generalized onset, and 2 (5.4%) unknown onset. The epilepsy type of 14 (37.8%) was focal epilepsy, 12 (32.4%) generalized epilepsy, 8 (21.6%) combined generalized-focal epilepsy, and 3 (8.1%) unknown epilepsy. Regarding the seizure control, 16 patient's (43.2%) seizures "controlled", 19 (51.4%) were "partially controlled" and 2 (5.4%) were "uncontrolled". The median dosage of LEV used to sustain seizure control was 19.35±9.16 mg/kg/day. There were non-significant differences detected in serum levels of HDL, LDL, TC, aspartate aminotransferase (AST), and alanine aminotransferase (ALT) of Group 1 compared to Group 2 (p=0.29, p=0.80, p=0.32, p=0.27, and p=0.44, respectively) (Table 2). The TG/HDL ratio was non-significantly higher in Group 2 (p=0.30).

The thyroid status of all the participants was between normal limits of their age (Table 2). Although all the participants' thyroid status was clinically euthyroid, Group 1 had mildly elevated FT4, TSH, and significantly elevated FT3 levels compared to Group 2 (p=0.41, p=0.52, and p=0.000, respectively).

Among Group 1, significant changes in uric acid and HDL levels between girls and boys were noted (girls: 3.5±0.84 mg/dL, boys: 4.7±1.4 mg/dL, girls: 61.6±13.3 mg/dL, boys: 52.2±11.3 mg/dL, p=0.003, and p=0.027, respectively). Although serum TG/HDL ratio, TG, ALT serum LDL, AST, TC levels tented to be increased, there were no significant difference had been shown between girls and boys (girls 1.87±1.07, boys 2.5±1.9, girls 108.4±53.7 mg/dL, boys 115.7±73.8 mg/dL, girls 14.3±5.1 mg/dL, boys 18.1±8.6 mg/dL, girls 84.4±25.9 mg/dL, boys 81.4±27.8 mg/dL, girls 27.1±12.7 mg/dL, boys 26.5±10.2 mg/dL, girls 164.4±21.8 mg/dL, boys 158.4±32.4 mg/dL, p=0.47, p=0.97, p=0.24, p=0.74, p=0.90, and p=0.33, respectively). The LDL, TC, and AST levels were significantly higher in pre-pubertal patients compared to pubertal ones (p=0.02, p=0.03, and p=0.018, respectively) (Table 3). But there were no significant difference in levels of uric acid, HDL, ALT, TG, TG/HDL ratio between pre-pubertal and pubertal patients (p=0.837, p=0.630, p=0.175, p=0.447, p=0.395, respectively). Also there was a non-significant difference in TG/HDL ratio between male and female gender of Group 1 (p=0.475).

Discussion

In the current study, we observed that epileptic children with LEV monotherapy had alterations in lipid metabolism. We had shown that patients treated with LEV had slightly elevated HDL, LDL, and TC without statistical significance. Especially the risk groups like males and prepubertal children should monitor closely for lipid metabolism alterations. Also, the thyroid hormone profile had changed in epileptic children with LEV monotherapy non-significantly.

Signs of atherosclerosis begin in childhood. Dyslipidemia is one of the leading risk factors for atherosclerosis. In general,

Table 2. Comparison of serum thyroid hormones, lipid profile, and other tests between two groups

Parameters	Group 1 (n=37)	Group 2 (n=54)	p-value
TSH mean ± SD Range (mIU/L)	2.04±0.70 0.81-2.95	1.94±0.83 0.30-4.44	0.52[a]
FT3 mean ± SD Range (pmol/L)	6.55±0.98 4.17-8.18	5.53±0.90 2.70-8.17	0.00[a]
FT4 mean ± SD Range (pmol/L)	16.86±4.89 11.4-35.06	16.29±4.23 10.80-28.70	0.41[b]
HDL mean ± SD Range (mg/dL)	57.03±13.07 34-86	54.27±11.65 25-76	0.29[a]
TG mean ± SD Range (mg/dL)	111.9±63.45 38-355	112.5±98.6 30-647	0.30[b]
LDL mean ± SD Range (mg/dL)	82.9±26.5 47-160	81.54±24.4 27-143	0.80[a]
TC mean ± SD Range (mg/dL)	161.5±27.3 119-218	154.23±25.3 93-220	0.32[b]
TG/HDL ratio mean ± SD Range	2.16±1.54 0.69-8.26	2.47±3.6 0.44-25.8	0.83[b]
AST mean ± SD Range (mg/dL)	26.8±11.4 12-50	23.9±10.4 11-66	0.27[b]
ALT mean ± SD Range (mg/dL)	16.2.±7.2 4-32	15.8±8.76 5-50	0.44[b]
Uric acid mean ± SD Range (mg/dL)	4.07±1.27 1.7-7.7	4.06±1.1 1.9-7.6	0.96[a]
CRP mean ± SD Range (mg/dL)	1.25±1.77 0.03-7.4	1.28±2.9 0.11-20.3	0.78[b]

TSH: Thyroid-stimulating hormone, FT3: Free triiodothyronine, FT4: Free thyroxine, TG: Triglyceride, TC: Total cholesterol, HDL: High-density lipoprotein, SD: Standard deviation, LDL: Low-density lipoprotein, AST: Aspartate aminotransferase, ALT: Alanine aminotransferase CRP: C-reactive protein, [a]: Normally distributed data were tested using the Student's t-test, [b]: Non-normally distributed data were tested using the Mann-Whitney U test.

A p<0.05 was considered statistically significant

Table 3. Comparison of serum lipid profile, and transaminase levels between pre-pubertal and pubertal epileptic children

Parameters	Pre-pubertal epileptic children (n=18)	Pubertal epileptic children (n=19)	p-value
HDL mean ± SD (mg/dL)	58.1±10.8	56±15.1	0.630[a]
TG mean ± SD (mg/dL)	101.9±48.8	121.5±74.9	0.447[b]
LDL mean ± SD (mg/dL)	92.9±24.9	73.4±24.9	**0.02[a]**
TC mean ± SD (mg/dL)	170±23.6	153±28.6	**0.03[b]**
TG/HDL ratio mean ± SD	1.9±1.3	2.4±1.8	0.395[b]
AST mean ± SD (mg/dL)	31.4±10.6	22.5±10.6	**0.018[b]**
ALT mean ± SD (mg/dL)	18.2±8.4	14.3±5.4	0.175[b]

TG: Triglyceride, TC: Total cholesterol, HDL: High-density lipoprotein, LDL: Low-density lipoprotein, AST: Aspartate aminotransferase, ALT: Alanine aminotransferase, SD: Standard deviation

[a]: Normally distributed data were tested using the Student's t-test, [b]: Non-normally distributed data were tested using the Mann-Whitney U test. A p<0.05 was considered statistically significant

serum concentrations of LDL and HDL levels are basic tests to determine atherogenicity at a young age[25]. Prior studies have noted the importance of the relationship between low concentrations of HDL, elevated concentrations of TG and LDL, and coronary artery disease. The HDL's protective effects on endothelial cells had attributed to its role in reverse cholesterol transport[9]. Previous studies investigating the association between dyslipidemia and LEV monotherapy has contradicting results. El-Farahaty et al.[20] demonstrated that LDL and HDL levels were higher in patients with LEV treatment concerning healthy controls. Karatoprak and Tosun[26] suggested that LEV affects the development of subclinical atherosclerosis in children despite normal lipid levels. Our results supported that serum levels of LDL, TC, transaminases and HDL were mildly elevated in patients with LEV monotherapy related to healthy controls. We also found suggestive evidence of lipid metabolism alterations in the males and pre-pubertal epileptic children receiving LEV. In contrast to these findings, some prior studies did not support that LEV monotherapy affects neither lipid profile nor thyroid function[8,18,19]. Kolekar et al.[27] claimed that LEV therapy did not cause lipid profile changes. Moreover, Attilakos et al.'s[5] follow-up study emphasized the favorable effect of LEV usage for 6-12 months reduced significant TG levels and TG/HDL ratio. Given these conflicting results in the literature and the relatively small sample size of the present study, further investigation requires to determine the association between lipid metabolism and LEV use.

In a recent study, Lee et al.[28] argue that the triglyceride/HDL ratio and the triglyceride-glucose index were alternative markers for metabolic syndrome in children. To the best of our knowledge, this is one of the few studies to target the TG/HDL ratio to evaluate changes in lipid metabolism in epileptic children treated with LEV. Our results showed that LEV use in epileptic children was incapable of being associated with an increased TG/HDL ratio relative to healthy children. But these data must be interpreted with caution because our sample size was a relatively small and heterogeneous group of epileptic children with varying duration of illness and LEV exposure. Further studies are needed to elucidate the effects of LEV on lipids in more detail by using TG/HDL ratio.

Prior studies have noted the unfavorable effect of traditionally used anti-seizure medications on thyroid dysfunctions[6]. In the literature, very little data scrutinizes the consequences of the second-generation anti-seizure medication effects on thyroid hormones in epileptic children. It is somewhat surprising that even though all the participants were in a euthyroid state, our results declared elevated levels of TSH, FT3, and free T4 levels in epileptic children using LEV monotherapy. The theoretical implications of these findings are unclear. A possible explanation for this might be the high prevalence of iodine deficiency in Turkey. We believe the clinical implications of our findings are important, although further work on these issues should be encouraged.

Study Limitations

The current study has some critical limitations. Firstly, the relatively small sample size prevents us from detecting significant conclusions. Secondly, the retrospective design of our research limited us from collecting the follow-up data of patients with LEV exposure. Also, we were incapable of obtaining neither the lipid profile nor the thyroid hormone status of the participants before the initiation of LEV. Because collecting this data was not compatible with our clinical

practice. To minimalize this effect, we recruited euthyroid participants with normal nutritional status for the study. We plan to circumvent these limitations with future research.

Conclusion

This study has identified that epileptic children receiving LEV therapy were slightly susceptible to dyslipidemia. Close monitoring of risky subgroups like pre-pubertal children and males is principally mandatory. Further studies are warranted to verify the side effects of long-term exposure to LEV in children and to clarify its influences of it on lipid metabolism and thyroid functions.

Information: ClinicalTrials.gov, protocol ID: 2021/186, ClinicalTrials.gov ID: NCT05276271, Name of the registery: The Effect of Levetiracetam on Lipid Profile in Children, URL: https://register.clinicaltrials.gov/prs/app/action/SelectProtocol?sid=S000BV88&selectaction=Edit&uid=U00061VL&ts=18&cx=2bpzlu.

Ethics

Ethics Committee Approval: The study was approved by the Balıkesir University Regional Ethics Committee (2021/186-08/09/21).

Informed Consent: The informed consent form was obtained from parents of all the participants.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: İ.D.Ç., M.D., Concept: İ.D.Ç., Design: İ.D.Ç., Data Collection or Processing: İ.D.Ç., Analysis or Interpretation: M.D., Literature Search: M.D., Writing: İ.D.Ç.

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