



Effect of levetiracetam monotherapy on lipid profiles and thyroid hormones in children with epilepsy: A prospective study

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ABSTRACT

Long-term treatment with some older antiepileptic drugs may lead to dyslipidemia or thyroid disturbances. The effect of levetiracetam (LEV), a newer broad spectrum antiepileptic agent, on cardiovascular risk factors is not yet sufficiently investigated. The purpose of this study was to investigate prospectively the effect of LEV monotherapy on serum lipid profile and thyroid hormones levels in children with epilepsy. The study population consisted of 39 children (21 females, 18 males, mean age 6.8 ± 4.1 years, range 2–15 years) that were treated for new-onset epilepsy with LEV monotherapy. Serum total cholesterol (TC), high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C), triglycerides (TGs), apolipoprotein A-I (apo A-I), apolipoprotein B (apo B), lipoprotein (a) [Lp(a)], thyroxine (T4), free thyroxine (fT4) and thyrotropin (TSH), were evaluated before and at 6 and 12 (n = 28) months of LEV monotherapy. TGs were significantly decreased at 6 and 12 months of LEV treatment (p = 0.026 and p = 0.001, respectively). TGs/HDL-C ratio was significantly decreased at 6 and 12 months of LEV treatment (p = 0.024 and p = 0.003, respectively), while LDL-C/HDL-C ratio was significantly decreased at 12 months of LEV treatment (p = 0.025). There were no significant alterations in the other parameters during the study. In conclusion, long-term LEV monotherapy does not cause adverse alterations on thyroid hormones and serum lipids in children with epilepsy. More studies are needed to clarify whether LEV monotherapy have a favourable effect on serum lipids and whether LEV may be considered as a safer alternative drug for the prevention of antiepileptic drug-induced cardiovascular complications in adult life.

1. Introduction

Long-term treatment with some older antiepileptic drugs, including sodium valproate and carbamazepine, may lead to dyslipidemia or thyroid disturbances (Katsiki et al., 2014; Hamed, 2015; Verrotti et al., 2009). Increases in serum lipid levels, particularly total cholesterol (TC), low-density lipoprotein cholesterol (LDL-C), triglycerides (TGs) and lipoprotein (a) [Lp(a)] or decreases in thyroxine (T4), free thyroxine (fT4) and subclinical hypothyroidism have been reported in both children and adults treated with older antiepileptic drugs (Katsiki et al., 2014; Hamed, 2015). The above changes in lipid and thyroid metabolism may increase cardiovascular risk in patients treated with antiepileptic agents (Delitala et al., 2017). Moreover, the increased mortality in patients with epilepsy has been associated with a worse cardiovascular risk profile (Shmueli et al., 2017).

Levetiracetam (LEV) is a new broad spectrum antiepileptic agent with favourable efficacy and low profile of toxicity in epilepsy treatment (Lyseng-Williamson, 2011). There are very limited and conflicting data about the effect of LEV monotherapy on serum lipids and thyroid hormone levels, especially in children with epilepsy. Higher LDL-C and LDL-C/HDL-C ratio and lower HDL-C, in a cross-sectional comparative study after LEV treatment, have been reported (El-Farahaty et al., 2015) while, in the only short-term prospective study, no significant alterations on serum lipids for a period up to 6 months, were reported (Nishiyama et al., 2019). Furthermore, in one cross-sectional and two prospective studies regarding the effect of LEV treatment on thyroid hormones, no significant changes or a lower mean fT4 have been reported (El-Farahaty et al., 2015; Nishiyama et al., 2019; Yilmaz et al., 2014). The purpose of this study was to investigate prospectively the long-effect of LEV monotherapy on serum lipids and thyroid hormone

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Table 1

Baseline characteristics of the study population (n=39) and the population finally analyzed at 12 months (n=28) of LEV treatment (presented as mean \pm SD).

Characteristics	Study population (n=39)	Population finally analyzed at 12 months (n=28)
Mean age (years, range)	6.8 \pm 4.1, 2-15	6.4 \pm 3.9, 2-14
Sex (female:male)	21:18	15:13
Height (cm)	121.1 \pm 24.2	120.8 \pm 25.9
Weight (Kg)	25.3 \pm 15.4	24.8 \pm 14.4
Body mass index (Kg/m ²)	17.1 \pm 2.8	16.8 \pm 2.8
Tanner staging		
Prepubertal	25	20
Pubertal	14	8
Seizure type		
Localized	29	22
Generalized	10	6

levels in children with epilepsy.

2. Materials and methods

The study was carried out in two tertiary pediatric referral centers in Athens, Greece. Subjects were derived from patients hospitalized for newly diagnosed epilepsy. The study population consisted of 39 children (21 females, mean age 6.8 \pm 4.1 years) that were treated for new-onset epilepsy with LEV monotherapy. Dropouts due to the need for add-on therapy with a second antiepileptic drug reduced the initial sample size to 28 patients at 12 months of LEV therapy (15 females, mean age 7.4 \pm 3.9 years). Baseline characteristics of the study population (n = 39) and the population finally analyzed at 12 months (n = 28) of LEV treatment, are shown in [Table 1](#).

LEV was prescribed at a dose of 10–35 mg/Kg/day. All patients had normal growth, normal liver and renal function and absence of any other medication or prior antiepileptic medication.

TC, LDL-C, TGs, HDL-C, apolipoprotein A-I (apo A-I), apolipoprotein B (apo B), Lp(a) T4, fT4 and thyrotropin (TSH) were measured before and at 6 and 12 months of LEV monotherapy. Lipids and apolipoproteins were measured using an automated analyzer (Roche Diagnostics Corporation, Indianapolis, Indiana, USA). Serum T4, fT4 and TSH were measured by electro-chemiluminescence immunoassays (Cobas, Roche Diagnostics Corporation, Indianapolis, Indiana, USA). The intra-assay and inter-assay coefficients of variation of all measured biochemical parameters was < 10%.

In all children, Tanner stage was defined, Body Weight (BW), Height (H) and Blood Pressure (BP) were measured and Body Mass Index (BMI)

Table 2

Changes in lipids, lipoproteins and thyroid hormone levels in children treated with levetiracetam monotherapy (data presented as means \pm SD).

	Baseline	6 th month of treatment (n=39)	p	12 th month of treatment (n=28)	p
TC (mg/dL)	163.1 \pm 26.3	162.4 \pm 27.7	0.986	159.7 \pm 30.8	0.985
HDL-C (mg/dL)	56.4 \pm 12.4	56.2 \pm 11.7	0.100	57.0 \pm 12.3	0.420
LDL-C (mg/dL)	99.6 \pm 23.4	102.6 \pm 37.2	0.778	92.3 \pm 28.5	0.164
TGs (mg/dL)	73.8 \pm 38.1	64.8 \pm 24.1	0.026	52.5 \pm 20.6	0.001
LDL-C/HDL-C	1.91 \pm 0.77	1.92 \pm 0.71	0.327	1.72 \pm 0.71	0.025
TGs/HDL-C	1.47 \pm 1.06	1.25 \pm 0.67	0.024	0.99 \pm 0.49	0.003
Apo A-I (mg/dL)	144.1 \pm 22.5	143.5 \pm 18.3	0.632	138.6 \pm 23.2	0.177
Apo B (mg/dL)	73.8 \pm 17.1	71.1 \pm 12.9	0.964	70.9 \pm 22.2	0.776
Lp(a) (mg/dL)	14.3 \pm 13.9	12.5 \pm 12.5	0.277	10.4 \pm 6.7	0.213
T4 (ng/dL)	8.57 \pm 1.27	9.20 \pm 2.43	0.058	8.78 \pm 1.56	0.486
fT4 (ng/dL)	1.32 \pm 0.18	1.37 \pm 0.35	0.790	1.37 \pm 0.13	0.349
TSH (μ IU/mL)	3.05 \pm 1.37	2.92 \pm 1.18	0.530	3.26 \pm 1.56	0.218
BMI-SDS	0.26 \pm 1.37	0.21 \pm 1.54	0.234	0.19 \pm 1.73	0.135

P indicates statistical differences between pre-treatment and after treatment levels.

Bold values indicate statistical significance (p < 0.05).

Abbreviations: Total cholesterol: TC; high-density lipoprotein cholesterol: HDL-C; low-density lipoprotein cholesterol: LDL-C; triglycerides: TGs; apolipoprotein A-I: apo A-I; apolipoprotein B: apo B; lipoprotein (a): Lp(a); thyroxine: T4; free thyroxine fT4; Thyrotropin: TSH; Body mass index standard deviation scores: BMI-SDS.

was calculated using the standard BMI = BW (Kg)/H² (m²). A standardized age- and sex-specific growth reference was used to calculate body mass index for-age standard deviation scores (BMI-SDS) (<http://www.quesgen.com/BMIPedsCalc.php>).

Written informed consent was obtained from all parents before participation and the study was approved by the local ethics committee. A blood sample was obtained after 10–12 hours of fasting, between 8.00 and 10.00 a.m.

Data were analyzed using the Statistical Package for the Social Sciences (SPSS, version 23.0, IBM Corp., Armonk, NY, USA). The Wilcoxon signed-ranks test was used to assess the significance of parameters at baseline and after treatment with LEV. Correlations among all the parameters and between the parameters and the LEV dose were assessed by using Spearman's correlation coefficient. A p value < 0.05 was considered statistically significant. A regression-based analysis of covariance (ANCOVA) was also performed to assess the potential effects of confounding factors such as age, sex, BMI-SDS, and LEV dose on the associations of parameters evaluated with LEV treatment. Post-hoc tests using Bonferroni correction were used to assess the potential for type I errors when performing multiple statistical tests. The multivariate analysis and Bonferroni correction were implemented using SAS (version 9, Cary, NC).

3. Results

The children participated in the study had an absolute response to the treatment. Twenty three of them required a minimal dose titration (up to 20 mg/kg) and 5 of them a significant dose titration up to 35 mg/kg. None of the children changed puberty stage during the study.

TGs were significantly decreased at 6 and 12 months of LEV treatment (p = 0.026 and p = 0.001, respectively). TGs/HDL-C ratio was significantly decreased at 6 and 12 months of LEV treatment (p = 0.024 and p = 0.003, respectively), while LDL-C/HDL-C ratio was significantly decreased at 12 months of LEV treatment (p = 0.025) ([Table 2](#)). There were no significant alterations in the other parameters evaluated during the study. Mean value of drug dose (mg/Kg) was 19.5 \pm 12.1 at 6 months and 21.9 \pm 12.8 at 12 months of LEV treatment.

No correlation was found between TGs or LDL-C/HDL-C ratio and the other parameters evaluated during the study. Among the confounding factors, none was found to be statistically significantly associated with TGs or TGs/HDL-C at 6 and 12 months of LEV treatment or with LDL-C/HDL-C ratio at 12 months of LEV treatment. There were no significant alterations in the post hoc tests using the Bonferroni correction.

4. Discussion

Our study showed no adverse significant effect of LEV monotherapy on serum lipids and thyroid hormones in children with epilepsy. Furthermore, serum TGs and TGs/HDL-C ratio were significantly decreased at 6 and 12 months of LEV treatment, while LDL-C/HDL-C ratio was significantly decreased at 12 months of therapy. No correlations were found between TGs, TGs/HDL-C or LDL-C/HDL-C ratio and LEV dose during the study period.

Data about the effect of LEV monotherapy on serum lipids, especially in children with epilepsy, are very limited and conflicting. In a cross-sectional comparative study, El-Farahaty et al. (2015) found significantly higher LDL-C and LDL-C/HDL-C ratio and lower HDL-C in 12 children (mean age 11.6 ± 1.9 years), when compared with healthy subjects, after LEV treatment for a period of 2.2 ± 0.45 years. Interestingly, in this study, LEV-treated children had the lowest mean TGs levels among the other antiepileptic-drug groups and the control group. Very recently, Nishiyama et al. (2019) in the only prospective short-term study in pediatric patients, reported no significant alterations on serum lipids in 12 children with epilepsy, after 1 and 6 months of LEV monotherapy.

Our study showed a possible favourable effect of LEV monotherapy on serum lipids in children with epilepsy. TGs and TGs/HDL-C ratio were significantly decreased at 6 and 12 months of LEV treatment while LDL-C/HDL-C ratio was significantly decreased at 12 months of LEV treatment. Individuals with high TGs/HDL-C or LDL-C/HDL-C index have greater risk for cardiovascular disease due to the imbalance between atherogenic and protective lipoproteins (Quijada et al., 2008; Millán et al., 2009). The changes in lipid profile observed in our study group may have a beneficial effect on later cardiovascular disease risk in children with epilepsy.

Recently, Mintzer et al. (2016) showed that switching patients from the enzyme-inducing agents, such as carbamazepine to non-inducing antiepileptic drugs, such as LEV, produces a reduction in serum cholesterol and C-reactive protein that is enduring, rather than the product of a temporary homeostatic reaction. The authors wondered whether these changes could be attributed to some lipid-lowering effect of non-inducing agents, including LEV. LEV specifically binds to synaptic vesicle protein (SV2A), which is commonly found in the central nervous system and endocrine tissues, suggesting that endocrine functions may be affected by LEV (Lyseng-Williamson, 2011). Our results showed a possible TGs-, TGs/ HDL- and LDL/HDL-lowering effects of LEV monotherapy in children with epilepsy but whether these effects exists and the mechanisms involved remains to be clarified in large prospective studies.

Our study showed no effect of LEV monotherapy on thyroid hormone levels, after one year of therapy. Similar to our results, in the other two longitudinal studies, Yilmaz et al. (2014) found no significant change of fT4 and TSH in 11 LEV-treated children aged 8.81 ± 3.78 years, at first, sixth and twelfth month of therapy, while Nishiyama et al.⁸ reported no significant alterations on fT4 or TSH in 12 children with epilepsy, after 1 and 6 months of LEV monotherapy. In contrast to above studies, El-Farahaty et al. (2015), in a cross-sectional study, found a significantly lower mean fT4 level in 12 children after LEV

treatment for a period of 2.2 ± 0.45 years, when compared with healthy subjects. Nevertheless, larger and prospective studies are needed to elucidate the effects of LEV treatment on thyroid hormone levels and whether these effects are of clinical significance.

Our study participants showed no significant changes in BMI-SDS during follow-up. This is in accordance with other studies that have found LEV to be weight neutral, in contrast with older antiepileptic drugs that may induce weight gain (Katsiki et al., 2014).

Our study has some limitations: the small number of patients studied and the absence of an untreated epilepsy group. Also, other cardiovascular parameters, such as dietary habits and physical activity were not addressed during the study period. The strengths of the present report are the homogeneity of the study group, the prospective design up to 1 year and that its prospective nature allows for evaluation of the same patients before and after treatment, eliminating possible confounders from sampling bias.

In conclusion, our study showed that, in contrast with older antiepileptic drugs, LEV monotherapy, up to one year in children with epilepsy, does not cause adverse alterations on thyroid hormones and possible have a favourable effect on serum lipids. Larger prospective studies are needed to definitely clarify the issue whether LEV may be considered as a safer alternative drug for the prevention of antiepileptic drug-induced cardiovascular complications in adult life.

References

- Delitala, A.P., Fanciulli, G., Maioli, M., Delitala, G., 2017. Subclinical hypothyroidism, lipid metabolism and cardiovascular disease. *Eur. J. Intern. Med.* 38, 17–24.
- El-Farahaty, R.M., El-Mitwalli, A., Azzam, H., Wasel, Y., Elrakhawy, M.M., Hasaneen, B.M., 2015. Atherosclerotic effects of long-term old and new antiepileptic drugs monotherapy: a cross-sectional comparative study. *J. Child Neurol.* 30, 451–457.
- Hamed, S.A., 2015. The effect of antiepileptic drugs on thyroid hormonal function: causes and implications. *Expert Rev. Clin. Pharmacol.* 8, 741–750.
- Katsiki, N., Mikhailidis, D.P., Nair, D.R., 2014. The effects of antiepileptic drugs on vascular risk factors: a narrative review. *Seizure* 23, 677–684.
- Lyseng-Williamson, K.A., 2011. Levetiracetam: a review of its use in epilepsy. *Drugs* 71, 489–514.
- Millán, J., Pintó, X., Muñoz, A., Zúñiga, M., Rubiés-Prat, J., Pallardo, L.F., Masana, L., Mangas, A., Hernández-Mijares, A., González-Santos, P., Ascaso, J.F., Pedro-Botet, J., 2009. Lipoprotein ratios: physiological significance and clinical usefulness in cardiovascular prevention. *Vasc. Health Risk Manag.* 5, 757–765.
- Mintzer, S., Miller, R., Shah, K., Chervoneva, I., Nei, M., Skidmore, C., Sperling, M.R., 2016. Long-term effect of antiepileptic drug switch on serum lipids and C-reactive protein. *Epilepsy Behav.* 58, 127–132.
- Nishiyama, M., Takami, Y., Ishida, Y., Tomioka, K., Tanaka, T., Nagase, H., Nakagawa, T., Tokumoto, S., Yamaguchi, H., Toyoshima, D., Maruyama, A., Nozu, K., Nishimura, N., Iijima, K., 2019. Lipid and thyroid hormone levels in children with epilepsy treated with levetiracetam or carbamazepine: a prospective observational study. *Epilepsy Behav.* 90, 15–19.
- Quijada, Z., Paoli, M., Zerpa, Y., Camacho, N., Cichetti, R., Villarroel, V., Arata-Bellabarba, G., Lanes, R., 2008. The triglyceride/HDL-cholesterol ratio as a marker of cardiovascular risk in obese children; association with traditional and emergent risk factors. *Pediatr. Diabetes* 9, 464–471.
- Shmueli, S., van der Lende, M., Lamberts, R.J., Sander, J.W., Thijs, R.D., 2017. The heart of epilepsy: current views and future concepts. *Seizure* 44, 176–183.
- Verrotti, A., Laus, M., Scardapane, A., Franzoni, E., Chiarelli, F., 2009. Thyroid hormones in children with epilepsy during long-term administration of carbamazepine and valproate. *Eur. J. Endocrinol.* 160, 81–86.
- Yilmaz, U., Yilmaz, T.S., Akinci, G., Korkmaz, H.A., Tekgul, H., 2014. The effect of antiepileptic drugs on thyroid function in children. *Seizure* 23, 29–35.