Child's Nervous System (2019) 35:769–774
https://doi.org/10.1007/s00381-019-04076-5

ORIGINAL ARTICLE

An investigation of the ocular toxic effects of levetiracetam therapy in children with epilepsy

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Received: 9 September 2018 / Accepted: 27 January 2019 / Published online: 20 February 2019

Abstract

Objective To investigate the potential toxic effects of levetiracetam monotherapy on ocular tissues in cases of pediatric epilepsy using optical coherence tomography (OCT).

Methods Thirty epileptic children (group 1) receiving levetiracetam monotherapy at a dosage of 20–40 mg/kg/day for at least 1 year with a first diagnosis of epilepsy and 30 age- and gender-matched healthy children (group 2) were included in the study. In addition to a detailed eye examination, peripapillary retinal nerve fiber layer (RNFL) thickness, ganglion cell complex (GCC) thickness, foveal thickness (FT), and central corneal thickness (CCT) were measured in all children by means of spectral domain OCT. The data obtained from the two groups were then subjected to statistical analysis.

Results The mean age of both groups was 12 ± 3.64 years [1–12]. The mean duration of levetiracetam in group 1 was 24.07 ± 12.82 months. Mean RNFL values in groups 1 and 2 were 106.1 ± 10.42 and 104.98 ± 10.04 μm, mean GCC values were 94.72 ± 6.26 and 94.4 ± 6 μm, mean FT values were 240.73 ± 17.94 and 240.77 ± 15.97 μm, and mean CCT values were 555.1 ± 44.88 and 540.97 ± 32.65 μm, respectively. No significant difference was determined between the two groups in terms of any parameter. Best corrected visual acuity values of the subjects in both groups were 10/10, and no color vision or visual field deficit was determined.

Conclusion Levetiracetam monotherapy causes no significant function or morphological change in ocular tissues in pediatric epilepsies.

Keywords Epilepsy · Optical coherence · Levetiracetam · Tomography

Introduction

Epilepsy is a common neurological disease thought to affect some 70 million people worldwide [13]. Visual alterations may develop in epilepsy due to the disease itself and also in association with antiepileptic drugs used in treatment [14].

Various antiepileptic agent options with different effect mechanisms are available in the treatment of epilepsy [15].

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A range of side-effects associated with the use of these drugs has been reported. One of the most common of these is visual dysfunction. Since the eye is highly sensitive to effect mechanisms, length of use, and dosages of several antiepileptic drugs, the use of antiepileptic agents can result in visual disturbances [16]. The main side-effects associated with the use of various antiepileptic drugs are diplopia, blurred vision, color disturbances, peripapillary retinal nerve fiber layer thickness attenuation, and visual field defects [1–4, 17].

Levetiracetam is a broad-spectrum antiepileptic drug frequently employed as monotherapy or as an adjunctive in pediatric patients with focal or generalized seizures due to its minimal drug interaction and the fact that it is well tolerated [5]. It exhibits a simple pharmacokinetic characteristic through being rapidly absorbed in the body [6]. It has a different effect mechanism to benzodiazepines, propofol, and barbiturates and possesses a dissimilar binding region. The effect of the drug emerges through modulation of synaptic neurotransmitter release by binding to the synaptic vesicle protein 2A in the brain [7, 8]. Levetiracetam does not modulate sodium, potassium, or calcium channels and is principally expelled from the body via the kidneys [9].

Optical coherence tomography (OCT) is an objective and noninvasive cross-sectional tissue-imaging technique that currently enjoys a wide sphere of use in ophthalmology [4, 10]. Several studies have described OCT as repeatable and reproducible, and have reported that the device can measure retinal and corneal thickness at the micrometer level while accurately reflecting changes in the retina and cornea [11]. OCT is thus important for clinicians in the clinical decision making process. Data elicited using OCT, including peripapillary retinal nerve fiber layer (RNFL) thickness, ganglion cell complex (GCC), retinal thickness, choroidal thickness, and central corneal thickness (CCT), play highly important roles in the diagnosis and monitoring of a large number of ocular and systemic diseases [10–12].

The effects of antiepileptic drugs on ocular tissue at the histological level are still not fully known. To the best of our knowledge, no previous studies have investigated potential changes in ocular tissue following levetiracetam use in the pediatric age group. The purpose of this study was to investigate potential functional and morphological changes in ocular tissues with levetiracetam use in cases of epilepsy.

Methods

Thirty epileptic children (group 1) aged 6–17 receiving levetiracetam monotherapy at a dosage of 20–40 mg/kg/day for at least 1 year with a first diagnosis of epilepsy and 30 age- and gender-matched healthy children (group 2) under monitoring in the neurology department were included in the study. Ethical approval was granted for the study. Informed consent was received from all children and their parents.

Cases with a history of premature birth; with any additional systemic disease other than epilepsy; with B_{12}, folic acid, or iron deficiency determined at routine blood tests; with secondary epilepsy; with any additional ocular pathology (such as strabismus, nystagmus, ptosis, corneal opacity, uveitis, cataract, glaucoma) other than refraction defect at ocular examination; with refractive error levels of spherical equivalent above ±4 D; with a cup/disc ratio ≥ 0.4 or asymmetry ≥ 0.2 in cup/disc ratios between the two eyes at optic nerve head examination; with intraocular pressure values above 21 mmHg; and with a previous history of eye surgery or trauma, or who refused to take part or who were unable to cooperate during examination were excluded from the study. Additionally, cases in which any other therapy apart from levetiracetam was required due to epilepsy or subjects who were unable to comply with levetiracetam therapy were also excluded.

All participants underwent detailed physical and neurological examinations. Complete routine blood tests were evaluated. The electroencephalography (EEG) records of epileptic children were also reviewed.

All participants underwent detailed eye examinations including refractive error, best corrected visual acuity (BCVA), and biomicroscopic anterior and posterior segment examinations, intraocular pressure (IOP) measurement, and color vision and perimetry evaluations. OCT examinations were performed in all cases meeting the inclusion criteria.

OCT examinations

An Optovue RTVue (RT100, software version 6.3, Optovue Inc., Fremont, CA) spectral domain IOCT device was used for this purpose. This device provides visualization and mapping of retinal microstructures at the histological level in vivo and a non-contact manner. In addition to detailed information concerning fundus and optic disc morphology, RTVue is also used to measure and map corneal layer thickness and topographic features [18]. This system operates at a 830-nm wavelength and is equipped with a scan speed of 26,000 A-scans/s and a depth resolution of 5 μm in tissue. Due to the benefits of higher speed and resolution, a complex scan protocol (GCC protocol) was developed for the macular region. This samples the macula in an even manner over a square area of 7 mm. The GCC scan pattern consists of a single horizontal line and 15 evenly aligned vertical lines at intervals of 0.5 mm. In this study, 14.928 A-scans were acquired over 0.6 s, after which an automated algorithm produced a thickness profile through segmentation of the GCC. This protocol was therefore employed to measure the GCC thickness in this study. We employed the optic nerve head (ONH) scan protocol to determine RNFL thickness. The ONH pattern is comprised of six

concentric circular scans ranging from 2.5 to 4 mm in diameter focused on the optic disc for RNFL calculation and of 12 radial scans of 3.4 mm focused on the disc for nerve head parameter calculation. The ONH protocol elicits a total of 9510 A-scans over 0.4 s [19]. The RNFL values obtained were recorded in the form of inferior, nasal, superior, and temporal quadrants and mean values for each subject. The macular cube scan (E-MM5) protocol was employed for FT calculation. The E-MM5 pattern is comprised of an external 6 × 6 mm grid consisting of 13 horizontal and 13 vertical lines, each of 668 A-scans, together with an inner 4 × 4 mm grid made up of 8 horizontal and 8 vertical lines, each of 400 A-scans. The inner 4 × 4 mm region is thus sampled with 250 μm between B-scans and 10 μm between A-scans in each B-scan [20]. The cornea anterior module pachymetry protocol is employed for CCT-related calculations. The cornea anterior module lens, which is applied to the anterior segment, permits a 6 × 6-mm corneal scan. The corneal image is aligned between the two red lines appearing on the monitor, the scan being acquired at the time when a high-reflective line passes through the center of the cornea [18]. All the pachymetry scans in this study were performed in the central 2-mm zone, and the pachymetry value determined was adopted as the CCT.

All OCT examinations were carried out by the same author, who was blinded to the study groups. The device's internal fixator was used to prevent children moving their eyes during OCT measurements.

Conditions of absence of artifacts in all scans, good demarcation of retinal and corneal tissues, and good measurement reliability rating with signal strength index (SSI) > 60 were imposed to ensure the reliability of the OCT scans used in the study.

Statistical analysis

Numerical data were expressed as mean ± standard deviation and descriptive data as number and percentage. Statistical analyses were performed on SPSS 13.0.1 software (SPSS, Chicago, IL, USA; license no. 9069728, KTU, Trabzon, Turkey). Data normality was assessed using the Kolmogorov-Smirnov test. Measurements between the groups were compared using the independent samples *t* test. $p < 0.05$ was considered statistically significant.

Results

The sex and age distributions of the participants were the same in the two study groups. Thirteen (43.3%) of the 390 subjects in both groups were girls and 17 (56.7%) were boys, and the mean ages were 12 ± 3.64 [1–12] years. There was thus no difference between the two groups in terms of age or sex. Demographic and clinical characteristics of patients with epilepsy are shown in Table 1. Types of seizure among the epileptic children in group 1 were generalized in 21 (70%) cases and focal in 9 (30%). EEG records for these cases revealed generalized epileptiform abnormality in 13 (43.3%) cases, focal epileptiform abnormality in 13 (43.3%), and were within normal limits in 4 (13.3%). The mean dose of levetiracetam in the epileptic children in group 1 was 25.97 ± 6.63 [20–40] mg/kg/day, and the mean duration of treatment was 24.07 ± 12.82 (12–72) months. No new epileptic seizure occurred in any subject during treatment.

Mean spherical equivalent refractive error values among the children in the study were similar in the two groups. Bilateral BCVA values were 10/10 in all subjects. Biomicroscopic anterior and posterior segment examinations, IOP, color vision, and perimetry evaluations were within normal limits in both eyes in all participants in both groups.

Eye examination findings from the two groups are shown in Table 2. All OCT assessments showing bilateral RNFL, GCC, FT, and CCT were similar in groups 1 and 2 ($p > 0.05$ for all parameters).

Discussion

The cornea is an avascular transparent tissue in the most anterior part of the eye [21]. The cornea is particularly important in terms of visual acuity and represents the principal refractive environment in focusing light rays reaching the eye onto retinal tissue. Agents compromising the structure of the transparent cornea are one of the main causes of loss of vision [22, 23]. Central corneal thickness is a parameter widely used to assess corneal health [24]. The absence of any significant difference in CCT values in the levetiracetam group in our study compared with the healthy control group, and a normal corneal morphology being observed at biomicroscopic anterior segment examination suggested that the drug has no toxic effect on corneal tissue.

Glial cells, including the astroglia and microglia, constitute a large percentage of the total cell population in the adult brain. These cells support neurons by providing trophic factors and the regulation of inflammatory and/or immunological processes [25]. One study reported that several antiepileptic drugs containing gabapentin, carbamazepine, lamotrigine, topiramate, oxcarbazepine, tiagabine, and levetiracetam affected the glial cells [25]. Another tissue containing glial cells is the retina and the optic nerve. On the basis of that study, antiepileptic drugs therefore have the potential to affect the retina and the optic nerve.

The retina is a particularly important tissue in terms of visual physiology and is where light entering the eye is converted to electrical potentials. The retinal tissue in the posterior part of the eye is regarded as a component of the central

Table 1 Demographic and clinical characteristics of patients with epilepsy

Characteristics	*N* (%)
Mean age (years)	12 ± 3.64 (6–17)
Male	17 (56.7%)
Types of seizure	Generalized 21 (70%)
	Focal 9 (30%)
EEG records	Generalized epileptiform 13 (43.3%)
	Focal epileptiform 13 (43.3%)
	Normal 4 (13.3%)
Dose of levetiracetam (mg/kg/day)	25.97 ± 6.63 (20–40)
Mean duration of treatment (months)	24.07 ± 12.82 (12–72)

nervous system as an anterior extension of the brain [26]. Retinal tissue contains photoreceptors, horizontal cells, bipolar cells, amacrine cells, ganglion cells, and Müller glia cells. The retina consists of three nuclear layers, an outer nuclear layer (ONL), an inner nuclear layer (INL), and a ganglion cell layer (GCL). These are interconnected by synapses [27]. Retinal ganglion cells include three separate layers in the retina, the retinal nerve fiber layer (RNFL) comprised of the ganglion cell axons, the ganglion cell layer (GCL) comprised of the ganglion cell bodies, and the inner-plexiform layer (IPL) comprised of the ganglion cell dendrites. These three together constitute the ganglion cell complex (GCC). Rod and cone photoreceptors in the ONL are the eye's light sensing cells and are responsible for black/white and color vision, respectively. Light rays are converted into neural signals as a result of the phototransduction cascade occurring in these cells. These signals are then processed by neurons in the inner retina and are transmitted to the upper centers of the brain as action potentials in the retinal ganglion cells that constitute the axons of the optic nerve [26]. The absence in this study of visual acuity, color vision, and perimetry deficit in the group receiving levetiracetam therapy shows that this drug does not cause any clinically significant functional loss in the neural cells described.

Glial cells carry out an important function in lesions and regeneration in the retina and optic nerve [28, 29]. Neurodegeneration that may occur for various reasons causes effects through astroglial activation and gliosis [30, 31]. Degeneration of neural structures in the visual pathway results in irreversible vision loss [27]. Oxidative stress occurring in association with various factors is thought to be involved in this degeneration [32]. Living cells are eliminated through necrosis or apoptosis, both of which can emerge as the result of various pathological stimuli [33, 34]. Several studies of animal models of retinal degeneration have suggested that apoptotic mechanisms can play a role in cell death [35, 36]. However, the regulation of apoptosis is still not completely understood. Studies have demonstrated that apoptosis is regulated by a large number of mediators [37, 38].

One study of the effect of valproic acid and levetiracetam on apoptosis in the human ovarian cancer cell line showed that valproic acid at concentrations exceeding 5 mM resulted in cellular changes associated with apoptosis and the caspase activation cascades. In contrast, administration of

Table 2 Eye examination results of epileptic children in the levetiracetam therapy group (group 1) and the healthy control group (group 2)

		Right eye			Left eye		
Parameters		Group 1	Group 2	*p* level	Group 1	Group 2	*p* level
Refractive error (*D*)		− 0.15 ± 0.6	− 0.03 ± 0.19	0.532	− 0.07 ± 0.66	0.02 ± 0.22	0.676
RNFL	Mean	106.1 ± 10.42	104.98 ± 10.04	0.673	107.24 ± 10.92	106.54 ± 11.35	0.808
	Inferior	130.83 ± 17.32	130.68 ± 16.65	0.973	137.4 ± 16.87	133.93 ± 16.49	0.424
	Nasal	80.95 ± 10.4	78.28 ± 12.55	0.374	79.85 ± 11.86	77.55 ± 13.48	0.537
	Superior	130.77 ± 17.75	129.39 ± 16.95	0.759	131.32 ± 18.1	134.95 ± 22.67	0.495
	Temporal	81.85 ± 12.31	81.53 ± 13.59	0.925	80.77 ± 11.33	79.77 ± 10.16	0.72
GCC (μm)		94.72 ± 6.26	94.4 ± 6	0.841	95.15 ± 6.2	94.74 ± 5.78	0.79
FT (μm)		240.73 ± 17.94	240.77 ± 15.97	0.994	241.77 ± 15.77	243.1 ± 13.37	0.725
CCT (μm)		555.1 ± 44.88	540.97 ± 32.65	0.168	553.83 ± 42.85	540.93 ± 30.17	0.183

RNFL, retinal nerve fiber layer; *GCC*, ganglion cell complex; *FT*, foveal; *CCT*, central corneal

levetiracetam at all the concentrations used in the study exhibited no association with mechanisms of apoptosis such as caspase activation [39]. These effects of valproic acid and levetiracetam on apoptosis were also determined in another study involving the human choriocarcinoma BeWo cell line [40]. That study even described long-term exposure to levetiracetam as leading to a decrease in caspase activity [40]. Another study evaluating the effects of levetiracetam on in vitro rat Schwann cells described the drug as protective due to its antiinflammatory, anti-oxidative, and anti-apoptotic properties [41].

One study using OCT to examine the effects of antiepileptic drugs use on RNFL reported relatively lower average and superior peripapillary RNFL thickness values in epileptic children using valproic acid at 10–40 mg/kg/day for at least 1 year compared with healthy subjects [42]. In our study, however, we observed no significant variation in RNFL, GCC, or FT values measured with OCT in pediatric cases receiving levetiracetam therapy compared with the healthy population. This was compatible with the apoptosis study findings described above.

Conclusion

This study was performed in order to evaluate potential morphological and functional changes in corneal and retinal tissue in epileptic children receiving levetiracetam. In conclusion, we observed no significant changes in retinal or corneal morphology in pediatric epileptic cases treated with levetiracetam. We also determined no clinically significant functional loss in the eyes of these patients.

Compliance with ethical standards Ethical approval was granted for the study. Informed consent was received from all children and their parents.

Conflict of interest The authors have no proprietary or financial interest in this study.

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