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Can the long term using of pregabalin in fibromyalgia affect the choroid and retinal nerve fiber layer?

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BACKGROUND: In this study, the effects of long-term pregabalin use on the choroid and retinal nerve fiber layer were investigated in the fibromyalgia disease.
METHODS: The patient group consisted of 41 fibromyalgia patients using pregabalin. The control group consisted of 41 newly diagnosed fibromyalgia patients who had not received any treatment yet. Choroidal and retinal nerve fiber layer thickness measurements were performed with Cirrus HD-OCT (Carl Zeiss Meditec Inc., Dublin, CA, USA) 30 minutes after pupil dilation with 1% tropicamide.
RESULTS: There was no difference in subfoveal choroidal thickness, nasal choroidal thickness and temporal choroidal thickness between the patient and control groups ($p > 0.05$). Increasing the duration of drug use within the patient group was found to thin the retinal nerve fiber layer ($p < 0.05$).
CONCLUSION: We found that pregabalin had no effect on the choroid, while it had a thinning effect for retinal nerve fiber layer. It is recommended not to be preferred pregabalin in fibromyalgia patients with retinal nerve fiber layer damage such as diabetic retinopathy and glaucoma. Patients treated with pregabalin should have regular control in the ophthalmology clinic.

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INTRODUCTION

Fibromyalgia (FM) is a clinical picture that includes many symptoms such as widespread chronic pain and fatigue, sleep disturbance, cognitive dysfunction, and depressive episodes [1]. The prevalence of fibromyalgia in the general population ranges from 0.2 to 6.6% [2]. Pregabalin is an α2-δ calcium channel ligand and has been approved by many countries such as the United States and Japan as the first choice in FM treatment [3].

It is known that various systemic diseases and topical or systemic drug use are associated with retinal toxicity [4]. Ocular side effects such as blurred vision, diplopia, ocular pain, photopsia and irritation have been reported for pregabalin which has a wide area of use such as the treatment of epilepsy, neuropathic pain and anxiety disorders, and can be used for many years, but its retinal and choroidal effects are still unknown [5].

The choroid consists of a vascular network that acts as a blood supply for the outer retina, optic nerve, and avascular fovea. The choroid has dense fiber plexuses innervated by both the sympathetic and parasympathetic parts of the autonomic nervous system. Additionally, there are primary afferent sensory fibers that lead to the trigeminal ganglion via the ophthalmic nerve [6]. Changes in choroidal circulation, autonomic nervous system inputs, or inflammation can lead to a change in choroidal thickness. Enhanced-depth imaging optical coherence tomography (EDI-OCT) allows fast and precise measurement of choroidal thickness. Therefore, the effects of various factors such as age, gender, smoking, and many local or systemic diseases on choroidal thickness have been evaluated in recent years [7]. In the literature, serous retinal detachment has been reported after the usage of high dose pregabalin, possibly due to increased choroidal vascular permeability caused by the effect of pregabalin [5].

Since the retina is an anatomical extension of the brain, it is thought that the retinal changes may occur in parallel with changes in the nervous system. Therefore, retinal nerve fiber layer (RNFL) examination with OCT has attracted considerable attention in terms of neurodegenerative diseases and effects of neurological drugs [8]. On the other hand, in rat retinas, α2-δ3 and α2-subunits were found in photoreceptors, bipolar cells, amacrine cells, and most cells in the ganglion cell layer of the retina [9]. We think that retinal interactions may occur with the pregabalin binding to the α2-δ subunits of presynaptic voltage-dependent calcium channels. There is no study yet reporting the effects of long-term pregabalin use on the retina and choroid. Therefore, in this study, we wanted to investigate the thickness changes that may occur in RNFL and choroid in chronic use of pregabalin.

MATERIAL-METHODS

This cross-sectional trial was performed at the Clinic of Ophthalmology, Orthopaedics and Traumatology and Rheumatology, Niğde Ömer Halisdemir University Hospital, between 2018 and 2020. The study protocol was approved by the Ethics Review

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Board of Niğde Ömer Halisdemir University Hospital and written consent was obtained from each patient before the eye examination. The study was conducted in accordance with the principles of the Declaration of Helsinki.

The study group was formed by selecting from the patients with a diagnosis of FM who were sent to our clinic for eye examination by the orthopaedics and rheumatology department of our hospital. The study included 41 FM patients who did not have any eye disease and were treated with only 300 mg pregabalin for patient group and 41 newly diagnosed FM patients who were not treated yet for the control group. The patient and control groups consisted of volunteers who did not have any eye pathology except refractive error, had full vision in both eyes, and were similar in age and gender. In both groups, patients with myopic, hyperopic, or astigmatic refractive errors greater than 3.0 dioptres (D), patients with ocular disease or ocular surgery, and patients who were under 18, pregnant, or breastfeeding were excluded from the study. Patients with systemic disease other than FM in both groups were also excluded from the study.

Age, gender, clinical information, and the detailed medical history of all cases were recorded. An ophthalmic examination including best-corrected visual acuity, slit-lamp biomicroscopy, intraocular pressure (IOP) measurements in primary gaze position with non-contact tonometry, fundus evaluation after pupil dilatation using a 90.0 D lens, colour vision, direct-indirect pupillary reactions, relative afferent pupil defect (RAPD), and eye movements was performed. There was a high correlation between the measurements of the right and left eyes, and the right eye measurements were taken in the patient and control groups.

Choroidal thickness measurement with EDI-Optical Coherence Tomography

Choroidal thickness measurement was performed with Cirrus HD-OCT (Carl Zeiss Meditec Inc., Dublin, CA, USA) 30 minutes after pupil dilation with 1% tropicamide.

HD 5 Line Raster protocol was reduced to a single line and shot. Images with signal strength lower than 6 were excluded in the study. The choroid was imaged in the Cirrus HD-OCT with EDI mode. The subfoveal choroidal thickness and choroidal thicknesses at points 500 µm, 1000 µm, and 1500 µm temporal and nasal to the fovea were measured. Temporal and nasal choroidal thicknesses were calculated by taking the average of 3 choroidal thicknesses measured at 500-1000-1500 micron intervals from the subfoveal region. Since manual measurements were made, measurements were repeated by two independent persons.

Retinal nerve fiber layer thickness measurement with Optical Coherence Tomography

RNFL thickness measurement was performed with Cirrus HD-OCT (Carl Zeiss Meditec Inc., Dublin, CA, USA) 30 minutes after pupil dilation with tropicamide 1%. Images with signal strength lower than 6 were excluded in the study. RNFL thickness is determined by an automatic computer algorithm without the need for a user or reference plane.

Statistical analysis

Statistical analysis was performed in STATA 14 package program. Numerical variables were summarized with mean ± standard deviation [minimum - maximum] values. Categorical variables were shown with numbers and percentages. Normality of numerical variables was examined by Kolmogorov Smirnov test, and homogeneity of variances was examined by Levene test. Whether there was a difference between the two groups in terms of numerical variables was done by *t* test in independent groups if parametric test assumptions were met. If not provided, it was examined using the Mann Whitney U test. Multiple regression analysis was used to reveal independent factors affecting choroidal and RNFL thickness. Pearson Correlation test was used to determine the intercorrelation between eyes. Power analysis was executed by using G*Power 3.1. The analysis was performed using a two-tailed test, a strong effect size ($d = 0.85$) and an alpha of 0.05, and resulted in a sample size of minimum 37 patients for each group to achieve a power of 0,95. $P < 0.05$ was accepted statistically significant.

Table 1. Demographic and clinical information of the study groups.

	Pregabalin group n:41	Control group n:41	*p*
Age (Avg ± SD)	65.68 ± 1.41	65.68 ± 1.26	0.458
Gender			0.803
Female N (%)	10 (24.39%)	11 (26.83%)	
Male N (%)	31 (75.61%)	30 (73.17%)	
Duration of the disease (Avg ± SD month)	50.46 ± 4.13	–	
Duration of the pregabalin treatment (Avg ± SD month)	40.95 ± 2.90	–	

SD: standard deviation

RESULTS

In Table 1, the difference between the patient and control groups in terms of age and gender was tested, and it was found that there was no difference between the groups (p: 0.458 and 0.803 respectively).

High correlation was found between the right and left eyes in subfoveal choroidal thickness (SFCT), nasal choroidal thickness (NCT), temporal choroidal thickness (TCT) and RNFL thickness. ($p = 0.000$, $r = 0.981$; $p = 0.000$, $r = 0.993$; $p = 0.000$, $r = 0.915$; $p = 0.000$, $r = 0.992$ respectively)

In Table 2, SFCT, NCT, TCT and RNFL values of the right eyes were compared between the pregabalin group and the control group (p: 0.788, 0.756, 0.562, 0.003 respectively). When we evaluated the p-value for statistical significance, the right RNFL value in the group using pregabalin was lower than the control group, and the difference between them was statistically significant.

In Table 3, the changes in the right eye values of the pregabalin group were tried to be determined using multiple linear regression analysis. In this analysis, after controlling the age and gender variables of the pregabalin group compared to the control group, we attempted to determine whether there was a statistically significant difference between the pregabalin group and the control group. Pregabalin use lost its statistical significance in terms of variables in the right eye (p: 0.180). It was determined that the age variable was negative and significant in almost all variables. This shows that as age increases, variables in the right eye are negatively affected.

In Table 4, the duration of drug used on FM patients taking pregabalin is used as an independent variable. When we look at the table, it was found that RNFL variables decreased as the duration of drug use was extended, and this decrease was statistically significant at the level of 1% (p: 0.000). No effect of the duration of medicine use on other variables was found. The RNFL results of male patients in the same age group according to the duration of drug use are illustrated in the Fig. 1.

When the pregabalin group was examined in terms of duration of drug use; there were 5 patients in between 0-12 months, 5 patients in between 12-24 months, 13 patients in between 24-36 months, 3 patients in between 36-48 months, and 15 patients in over 48 months.

Table 2. Comparison of Choroidal and RNFL Thicknesses Between Groups.

	Pregabalin group (n = 41)	Control group (*n* = 41)	*p*
Right subfoveal choroidal thickness (μm)	258.75 ± 5.90	258.87 ± 4.82	0.788
Right nasal choroidal thickness (μm)	234.24 ± 6.09	233.78 ± 4.09	0.756
Right temporal choroidal thickness (μm)	243.56 ± 6.21	240.17 ± 5.13	0.562
Right RNFL thickness (μm)	80.02 ± 2.02	83.48 ± 1.30	0.003

Table 3. Multiple linear regression analysis for pregabalin group and control group.

	Right nasal choroidal thickness (p)	Right subfoveal choroidal thickness (p)	Right temporal choroidal thickness (p)	Right RNFL thickness (p)
Pregabalin Group	1.212 (0.867)	0.231 (0.974)	5.220 (0.481)	−1.974 (0.180)
Age	−0.800 (0.023)	−0.616 (0.121)	−1.577 (0.000)	−0.952 (0.000)
Gender	−15.67 (0.004)	−21.259 (0.000)	−16.431 (0.011)	5.773 (0.005)
Constant	305.07 (0.000)	325.441 (0.000)	362.356 (0.000)	137.40 (0.000)

Table 4. Effect of pregabalin usage time on choroidal and RNFL thickness.

	Right Nasal Choroidal Thickness (p)	Right Subfoveal Choroidal Thickness (p)	Right Temporal Choroidal Thickness (p)	Right RNFL Thickness (p)
Duration of use	0.237 (0.386)	0.096 (0.616)	0.216 (0.354)	−0.482*** (0.000)
Constant	224.506*** (0.000)	254.809*** (0.000)	235.055*** (0.000)	99.751*** (0.000)
N	41	41	41	41
R-square	0.013	0.002	0.021	0.477

** and *** indicate statistical significance at 5% and 1% levels, respectively.

DISCUSSION

To our knowledge, our study is the first study evaluating the effect of chronic pregabalin usage on choroid and RNFL in FM patients. While no effect of long-term drug use on choroid was observed in our study, a significant thinning in RNFL was detected. Although thinning was detected in RNFL in comparison to the control group, no significant difference was found in the multiple regression analysis. This may be due to the higher number of patients using drugs for less than 4 years in the pregabalin group.

Although the mechanism of action of pregabalin is not fully understood, it is explained by the fact that it reduces the release of many excitatory neurotransmitters such as glutamate, noradrenaline and substance P by modulating the depolarization-induced calcium flow [10]. It has also been shown to reduce sympathetic nervous system activity and inhibit sympathetically sustained pain [11]. Parveen et al. reported that oral pregabalin could be an effective premedication to alleviate the sympathetic response to tracheal intubation [12]. The choroidal circulation, which is structurally composed of branches of the ciliary arteries, is controlled neurogenically, unlike retinal vessels. Sympathetic innervation includes noradrenergic and neuropeptide fibers, while parasympathetic nerves are mainly cholinergic. Therefore, local mediators and sympathetic and parasympathetic systems are thought to play a role in changing choroidal thickness. In other words, inflammatory or pharmacological factors that might affect the autonomic nervous system may affect the choroid and cause perfusion changes [13]. Toledo et al. reported that the activity of Edinger-Westphalia nucleus neurons, which are responsible for the control of miosis and choroidal blood flow in birds, is mediated by glutamate [14]. Cuthbertson et al. showed that ciliary ganglion innervation affects choroidal blood flow in the upper and temporal parts of the eye in pigeons [15]. de Hoz R et al. reported that substance P positive intrinsic choroidal neurons are abundant especially in the central choroid and peripheral sensory innervation may play a role in this mechanism while regulating choroidal blood flow [16]. The choroidal blood flow and hence the thickness of the choroid are likely to be affected, since pregabalin reduces sympathetic system activity and reduces the release of many excitatory neurotransmitters such as glutamate, noradrenaline and substance P. To the best of our knowledge, there is no study examining the interaction between choroid and pregabalin in the literature. But Tanyıldız et al. mentioned that serous retinal detachment occurred by the increase in choroidal vessel permeability due to the use of high-dose pregabalin [5]. In our study, which we planned in line with this information, we did not see any effect of drug use on the choroid.

In recent years, measurement of RNFL thickness with OCT has become a valuable diagnostic tool to detect the effect of various drugs and neurodegenerative diseases in the retina [17–19]. Since the retina is of neuroectoderm origin, it has been reported that α2-δ subunits, which are the target of pregabalin, are found in photoreceptors, bipolar cells, amacrine cells and the ganglion cell layer of the retina [9]. However, there is no study that directly examines the effect of the pregabalin on RNFL. The effect of pregabalin in ocular areas such as diabetic retinopathy and glaucoma has been studied [20–22]. Ali et al. reported that in diabetic retinopathy in rats, pregabalin partially alleviated retinal apoptosis by reducing glutamate, and therefore pregabalin can be used in the treatment of diabetic retinopathy [20]. Moriya et al. reported the neuroprotective effects of pregabalin in a rat facial nerve avulsion model [23]. Ibrahim et al. mentioned the effect of pregabalin in reducing eye tension, and perhaps this result may have an effect that can prevent RNFL thinning in glaucoma [22]. Despite the neuroprotective effects of pregabalin reported in the literature, there are also studies reporting that the drug is neurotoxic. In a study investigating the effects of long-term and

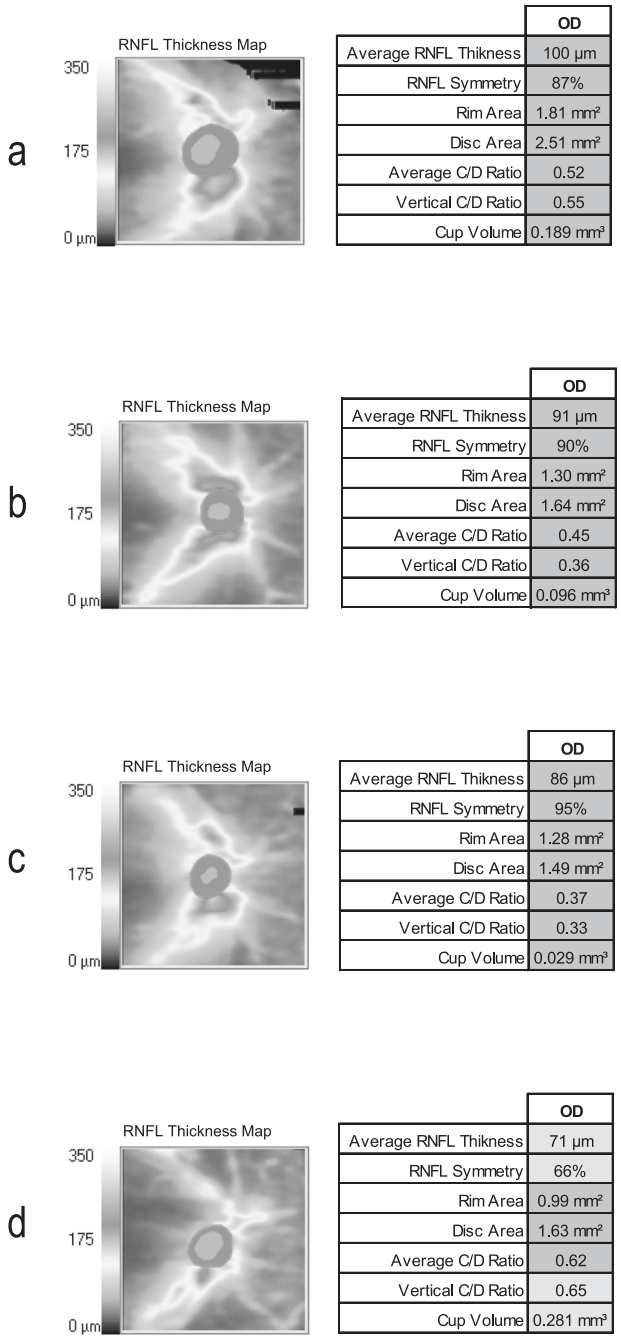

Fig. 1 Examples of RNFL thickness in terms of duration of using pregabalin. a Right RNFL image of 52-year-old male patient newly diagnosed with FM. **b** Right RNFL image of 49-year-old male patient treated with pregabalin for 2 years. **c** Right RNFL image of 53-year-old male patient treated with pregabalin for 4 years. **d** Right RNFL image of 56-year-old male patient treated with pregabalin for 6 years.

high-dose pregabalin use in rats, it was found that pregabalin increased oxidative stress and induced neuronal apoptosis in cerebral cortical tissue [24]. In a very recently published study, chronic use of pregabalin in rats was examined and it was found that chronic drug use increased apoptosis and gliosis as a result of oxidative stress in histological frontal cortex samples [25]. Kamel reported the neurotoxic effects in chronic use of pregabalin in rat brains [26]. Ninomiya et al. mentioned the retinal dysfunction effect of pregabalin. They showed that 10 months of pregabalin use can cause erroneous synaptic transfer from rod/cone photoreceptors to bipolar cells in the patient [27]. In addition, retinal teratogenicity of pregabalin in the chick embryo model was investigated by Seçinti, and it was reported that the use of pregabalin during pregnancy may be teratogenic due to damage to the retinal layers [28]. Considering the literature studies, it is highly probable that pregabalin has an effect on retinal cells, but no definite information has yet been revealed in terms of its mechanism of action and results. This may be due to the fact that its effect occurs by reducing the release of multiple neurotransmitters and this multifactorial situation also leads to more complex results. In our study, we found a significantly thinner RNFL in contrary to the protective effect.

What needs to be mentioned in our study is literature studies reporting that FM affects choroidal thickness and RNFL. Ulusoy et al. showed that choroidal thickness decreased in patients with FM and was associated with disease activity [29]. Garcia-Martin et al. reported that FM was associated with RNFL thinning [30]. However, in both studies, the medical treatment patients received was not mentioned. It is doubtful that this effect is due to FM.

One of the confounding factors in our study; since the control group consisted of newly diagnosed FM patients, the similarity between the two groups in terms of disease duration is doubtful. It was impossible for us to determine how long the newly diagnosed patients had been suffering from the disease. If we were to create a similar group in terms of disease duration from the moment of diagnosis, this time other pharmacological agents used in the treatment would have interacted. However, since the eye effects of FM are not certain, this cannot be said to be a definite limiting factor. In the statistical results made considering these conditions, we found that the use of pregabalin did not affect the choroid and RNFL in the comparison between the patient and control group. But in the multiple regression analysis performed in the pregabalin group, the duration of drug use appears as an independent risk factor in RNFL examination.

The small sample size is one of the main limitations of our study. We had to complete our study with small study groups because the prevalence of FM was not common and the exclusion of patients with systemic diseases and the eye pathologies.

Another limitation of the study was the manual measurement of choroidal thickness. Therefore, in our study, evaluations were made and compared by two independent researchers to check the reliability.

As a result, prolonged use of pregabalin, whose mechanism of action is mixed, has no effect on the choroid, while it has a thinning effect for RNFL. For this reason, it is recommended not to be preferred in patients with RNFL damage such as diabetic retinopathy and glaucoma when choosing drugs in FM patients. Patients receiving pregabalin treatment should be regularly examined in the ophthalmology clinic.

SUMMARY

What was known before

- Before our study, there was no study about the effects of pregabalin on the choroid and RNFL

What this study adds

- In our study, it was found that pregabalin did not affect the choroid and it was observed that it thinned the RNFL in chronic use. We think that pregabalin use should not be preferred in individuals with diseases affecting RNFL such as glaucoma.

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AUTHOR CONTRIBUTIONS

GYB was responsible for the study design, data collection and analysis, writing of the. manuscript and creation of the figures. KRZ and KEB were responsible for parts of the data collection. EK and EBK were responsible for manuscript review. The final version was of the manuscript was approved by all authors.

COMPETING INTERESTS

The authors declare no competing interests.

ADDITIONAL INFORMATION

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