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ORIGINAL ARTICLE

Evaluation of inner retinal layers with optic coherence tomography in vigabatrin-exposed patients

Betül Tuğcu[1] · **Mesrure Köseoğlu Bitnel**[2] · **Fatma Selin Kaya**[3] · **Betül Tekin Güveli**[2] · **Dilek Ataklı**[2]

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Abstract In order to reveal the underlying retinal pathology leading to dysfunction in vigabatrin-exposed patients, we aimed to evaluate the inner retinal layers encompassing ganglion cell complex (GCC) layer and inner plexiform layer with new generation optic coherence tomography (OCT). Fourteen patients with epilepsy and exposure to vigabatrin and 12 clinically normal individuals, constituting the control group, were included. Retinal images were obtained using spectral-domain OCT (Optovue RTVue Fourier domain). Nasal and superior quadrants of retinal nerve fiber layer (RNFL) were found to be significantly lower in the patient group compared to the controls ($p < 0.01$). No significant difference was shown in the thickness of GCC layer ($p > 0.05$). Foveal thickness was significantly higher in the patient group (p: 0.006), but no significant difference was found in perifoveal and parafoveal regions between groups ($p > 0.05$). The thickness of RNFL was found to be lower in vigabatrin-exposed patients without any reduction in GCC layer in the macular region. However, foveal thickness was found to be significantly higher compared to perifoveal and parafoveal macular regions in vigabatrin-exposed patients. In conclusion, OCT revealed reduced thickness of RNFL without any reduction in ganglion cell layer in our study. The objective quantitative assessment of OCT is a practical noninvasive method and it can have role in future monitoring of these patients.

Keywords Optic coherence tomography · Vigabatrin · Retina · Epilepsy · Anticonvulsants

Introduction

Vigabatrin (VGB) is an anti-epileptic drug used as adjunctive therapy for the treatment of epilepsy. Its adverse effects on the visual system limit its usage to only the very severe cases where all combinations of anti-epileptic drugs have proved ineffective. Vigabatrin is associated with asymptomatic visual field loss with unknown mechanism. Several theories have been suggested about the cause, such as accumulation of gamma amino butyric acid (GABA) in the retina and dysfunction in the GABA innervation of the retina [1, 2]. Besides, postmortem studies have indicated extensive losses of retinal ganglion cells (RGC) and their axons [3]. Asymptomatic long-term visual toxicity has been reported to be present even after discontinuation of drug therapy [4]. To date, the role of the drug dose in VGB-induced toxic retinopathy has been uncertain, and the role of genetic variation has been suggested [5].

Visual field examination is recommended for screening of VGB toxicity; however, serial monitoring of visual field is difficult in these patients because of age and impaired cognition and attention due to their seizures [5]. Visual electrophysiology has been shown to be effective in testing of visual field loss particularly in noncooperative patients, but it has been suggested as a time-consuming method with a requirement of a high-level operator expertise [6]. Recently, examination of the retinal nerve fiber layer (RNFL) using optic coherence tomography (OCT) has been proposed as an alternative method for screening of VGB toxicity [7, 8]. New generation spectral-domain OCT, having a

✉ Betül Tekin Güveli
betultekin2013@gmail.com

[1] Department of Ophthalmology, Bezmialem University Medical Faculty, İstanbul, Turkey

[2] Department of Neurology, Bakirkoy Research and Training Hospital for Psychiatry, Neurology, Neurosurgery, Bakırköy, 34147 Istanbul, Turkey

[3] Department of Eye Clinic, Bakırköy Dr. Sadi Konuk Research and Training Hospital, İstanbul, Turkey

shorter scanning time with high repeatability and reproducibility, can be performed safely and reliably on learning disabled patients [9–11]. Nevertheless, there were limited studies only evaluating peripapillary RNFL thickness about retinal toxicity of VGB [8, 12, 13]. In our study, in addition to the assessment of RNFL, in order to reveal the underlying retinal pathology leading to dysfunction, we aimed to evaluate the inner retinal layers encompassing ganglion cell complex (GCC) layer and inner plexiform layer with new generation OCT.

Patients and methods

This study included 14 patients with epilepsy and exposure to VGB as an adjunctive therapy. The patients were recruited from the epilepsy outpatient clinic of Bakirkoy Research and Training Hospital for Psychiatry, Neurology, Neurosurgery. Clinical data including history of exposure to VGB, duration of therapy, and estimated cumulative dose were obtained from the medical notes. Inclusion criteria were the absence of visual alterations and ocular comorbidities along with the diseases affecting the retina and optic nerve (diabetes mellitus, glaucoma, and optic neuropathy), no previous ocular surgery and trauma. Twelve clinically normal individuals with similar age and sex constituted control group.

All patients underwent a complete ophthalmological examination. Standard automated visual perimetry was attempted on all patients. OCT examination was performed in Ophthalmology Clinic of Bakirkoy Dr. Sadi Konuk Research and Training Hospital. Patients who were not able to cooperate with OCT examination were excluded from the study. Retinal images were obtained using spectral-domain OCT (Optovue RTVue Fourier domain, RTVue-100, 2007, version 3.0, Optovue Inc., Fremont, CA, USA). The patients were also selected on the basis of their ability to maintain steady fixation at the OCT, and each scan was accurately checked to avoid misalignment of foveal imaging. All retinal scans were performed by the same examiner. Throughout scanning, the subject kept each eye constantly fixed on an internal target provided by the equipment. All scans had a signal strength of at least 50 (30–79.4). Each eye underwent NHM4, MM5, and GCC scan protocols. MM5 scan protocol measures the macular retinal thickness map with a 5×5 mm^2 grid centered on fixation. The map of macular thickness was composed of three concentric circles: a central circle (fovea), an inner ring (parafovea), and an outer ring (perifovea). NHM4 scans (4 mm diameter) measure RNFL thickness and the optic disc. The GCC scan protocol measures the GCC layer, which encompasses the RNFL, ganglion cell bodies, and inner plexiform layer. It has one horizontal line of 7 mm in scan length, followed by 15 vertical lines of 6 mm scan lengths, and 0.5 mm intervals, centered 1 mm temporal to the fovea.

Statistical analyses were performed using NCSS (Number Cruncher Statistical System 2007, Kaysville, UT). Descriptive statistical methods were used for the assessment of data. Student's *t* test was used for the comparison of parameters with normal distribution between the patient group and control group. Pearson correlation coefficient was performed for the correlation of the OCT parameters with the duration and cumulative dose of the drug. The significance level was set at a *p* value of less than 0.05.

The study was approved by the local ethical committee, and written informed consent was received from all patients. The study was performed according to the tenets of the Declaration of Helsinki for research involving human subjects.

Table 1 Assessment of temporal and superior quadrants of RNFL between the groups

	Mean of RNFL (μ)		
Quadrants	Patient	Control	P
Temporal	84.81 ± 13.75	88.96 ± 18.67	0.373
Temporal Lower	83.08 ± 12.40	82.50 ± 18.87	0.900
Temporal Upper	86.62 ± 17.99	95.46 ± 20.08	0.107
Superior	118.50 ± 23.27	144.33 ± 14.57	0.001**
Superior Temporal	130.38 ± 28.87	161.13 ± 16.93	0.001**
Superior Nasal	106.8 ± 120.53	127.46 ± 14.36	0.001**

RNFL retinal nerve fiber layer

Student's *t* test *$p < 0.05$, **$p < 0.01$

Results

The study was performed on 26 participants. All participants had normal visual acuity and color vision. Fundus examination did not reveal optic nerve or retinal pathology in any of the patients. Visual field testing was not possible due to patient noncooperation in patient group.

Mean age was 32.96 ± 12.95 (16–60) years; no significant difference was found between patient group (33.33 ± 12.62)

Table 2 Assessment of nasal and inferior quadrants of RNFL between the groups

	Mean of RNFL (μ)		
Quadrants	Patient	Control	*P*
Nasal	73.42 ± 16.00	89.96 ± 14.76	0.001**
Nasal Upper	74.46 ± 16.53	92.58 ± 16.63	0.001**
Nasal Lower	72.65 ± 17.02	87.46 ± 14.87	0.002**
Inferior	134.15 ± 26.01	143.58 ± 17.39	0.136
Inferior Nasal	123.15 ± 28.36	137.92 ± 18.82	0.034*
Inferior Temporal	148.58 ± 31.21	149.17 ± 23.46	0.941

RNFL retinal nerve fiber layer

Student's *t* test *$p < 0.05$, **$p < 0.01$

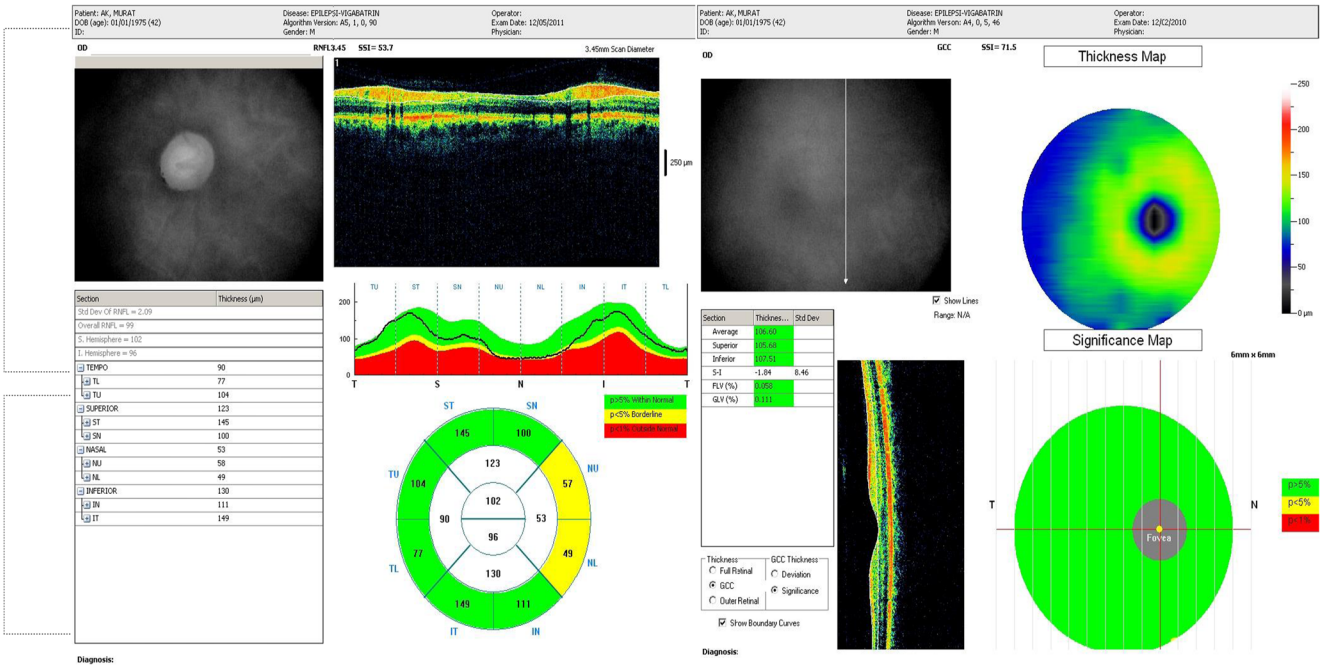

Fig. 1 Patient showing nasal thinning of retinal nerve fiber layer and normal ganglion cell complex values

and control group (33.35 ± 12.40) ($p > 0.05$). There were 13 (50%) males and 13 (50%) females (patient group: seven males and seven females; control group: six males and six females). There were five patients with unknown epilepsy, and nine patients with structural/metabolic epilepsy. Duration of disease was 18 ± 9.1 (2–28) years.

The mean age at which drug is received was 25.82 ± 10.43 (14–51). The mean duration of VGB therapy was 52.07 ± 43.59 (2–163) months. The mean cumulative dose of VGB was 1409.09 ± 436.93 mg, and the range of daily dose was 1000–2000 mg.

During OCT assessment, nasal quadrants of RNFL thickness (nasal, upper and lower nasal) were found to be significantly lower in the patient group compared to the controls ($p < 0.01$). Similarly, superior quadrants of RNFL in the patient group were found to be significantly lower compared to the control group ($p < 0.01$). However, RNFL measurements of temporal and inferior quadrants do not exhibit significant differences between patient and control groups ($p > 0.05$). Additionally, while there was no significant difference in the values of RNFL thickness in the inferior and inferior temporal quadrants between groups, inferior nasal RNFL thickness was significantly thinner in the patient group (p: 0.034) (Tables 1 and 2) (Fig. 1).

The retinal thickness of the macular region was assessed in three concentric circles by OCT examination. Foveal thickness was significantly higher in the patient group (p: 0.006), but no significant difference was found in perifoveal and parafoveal regions between groups ($p > 0.05$). When we analyze GCC layer, we could not find any difference in the total, superior, and inferior GCC measurements ($p > 0.05$) (Table 3).

We also investigated for any association among patient data and OCT parameters. The duration and cumulative dose of VGB were not significantly correlated with the thickness of retina and GCC layer (Pearson correlation coefficient, $p > 0.05$) (Table 4).

Discussion

In this study, consistent with the literature, RNFL thinning with preservation in the temporal quadrant was found to be significantly lower in the VGB-exposed patients compared to the controls [10, 13]. This tissue loss of the nasal, superior and inferior parts in optic nerve head has been named as "C shaped" or "inverse atrophy " or "temporal sparing atrophy", and it is different from the temporal and macular atrophy

Table 3 Assessment of macula and GCC between the groups

	Patient	Control	*P*
Fovea	265.12 ± 16.75	251.71 ± 15.99	0.006**
Perifovea	302.00 ± 23.28	294.00 ± 8.86	0.113
Parafovea	318.42 ± 28.03	325.63 ± 11.21	0.235
GCC total	102.85 ± 11.03	99.21 ± 4.67	0.133
GCC superior	102.27 ± 10.88	99.00 ± 5.49	0.183
GCC inferior	103.65 ± 11.87	99.58 ± 4.18	0.111

GCC ganglion cell complex

Student's *t* test **$p < 0.01$

Table 4 The correlation of the OCT parameters with the duration and cumulative dose of the vigabatrin

		Nasal RNFL	Temporal RNFL	Superior RNFL	Inferior RNFL	GCC total	GCC superior	GCC inferior
Age	PC	−0.063	0.101	0.103	−0.271	0.096	0.119	0.055
	P	0.853	0.747	0.763	0.420	0.779	0.729	0.873
Duration of therapy	PC	−0.566	−0.180	−0.375	−0.322	−0.066	−0.06	−0.061
	P	0.070	0.597	0.265	0.344	0.847	0.86	0.858
Cumulative dose	PC	−0.271	−0.379	−0.277	−0.086	−0.193	−0.178	−0.192
	P	0.420	0.251	0.464	0.801	0.57	0.602	0.573

PC Pearson correlation coefficient, *RNFL* retinal nerve fiber layer, *GCC* ganglion cell complex

which is seen more commonly in other toxic optic neuropathies [13]. Additionally, in a postmortem study from a single VGB-exposed individual with visual field loss, severe ganglion cell loss, and RNFL atrophy were demonstrated in the peripheral retina [14].

There is no clear evidence as to whether RGC damage is the primary event for VGB toxicity, or whether RGC loss occurs secondary to other retinal cell dysfunction. In VGB-exposed animal studies, severe disorganization and degeneration of photoreceptors has been reported as the most prominent change [15, 16]. Conversely, significant RGC loss has been reported in VGB-exposed neonatal rat, and it is proposed that RGC loss is a primary consequence of VGB toxicity and does not occur secondary to photoreceptor degeneration [14]. The macula is relatively spared, although superficial retinal light reflexes indicating wrinkling of the innermost retina suggest early macular toxicity [17]. Besides, one case report described a patient who had visual deterioration and showed pronounced bilateral optic atrophy and maculopathy [18]. To the best of our knowledge, in literature, there was no study assessing RGC with OCT in VGB-exposed patients. In our study, we found reduced thickness of RNFL without any reduction in GCC layer in the macular region. However, when we analyzed full-thickness retina in the macula, foveal thickness was found to be significantly higher compared to perifoveal and parafoveal macular regions in VGB-exposed patients. Fovea contains only cones and processes of Müller cells. In literature, morphological changes in Müller cells and severe degeneration of photoreceptors have been reported in experimental animal studies [19]. Additionally, effect of VGB on electroretinal functions at the level of Müller cells, and postreceptor cone system has been concluded [20, 21].

The main limitation of this study is the small sample size, and we can draw no conclusions with only 14 patients. However, to the best of our knowledge, this is the first study investigating macular RGC layer with OCT in VGB-exposed patients. While there was no significant change in RGC layer in the macular region, foveal thickness was found to be increased compared to perifoveal and parafoveal macular region. These preliminary results give further insight into the pathological changes related to VGB-induced toxicity. Further studies are warranted in order to constitute the underlying pathology in VGB-induced toxicity.

In conclusion, OCT revealed reduced thickness of RNFL without any reduction in ganglion cell layer in our study. The objective quantitative assessment of OCT is a practical noninvasive method. Additionally, it can have a role in future monitoring of these patients due to its reliable quick evaluation.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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