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ORIGINAL ARTICLE

Correlation between structural and functional tests in primary open-angle glaucoma

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Abstract

Purpose: The objective of this study was to evaluate the correlation between functional (visual field and visual evoked potentials [VEP]) and structural (optical coherence tomography [OCT]) test findings in primary open-angle glaucoma (POAG) patients.

Methods: A total of 56 eyes of 28 patients with POAG were tested. A complete ophthalmological examination, with a visual field test, OCT exam, and VEP recording, was performed. Measurements of the intraocular pressure, N75-P100 amplitude, N75 and P100 latency of VEP, retinal nerve fiber layer (RNFL) and ganglion cell complex (GCC) thickness, mean deviation (MD), pattern standard deviation (PSD), and visual field index (VFI) of the visual field were recorded. The parameters were assessed for correlations.

Results: The RNFL and PSD parameters were negatively correlated (r=-0.324, p=0.015). The RNFL was positively correlated with the N75-P100 amplitude (r=0.586, p=0.000). The GCC demonstrated a positive correlation with the MD and a negative correlation with the PSD (r=0.431, p=0.001; r=-0.264, p=0.049, respectively). The P100 latency and the VFI were negatively correlated (r=-0.344, p=0.009). The N75 latency was positively correlated with the RNFL and the GCC (r=0.375, p=0.004; r=0.324, p=0.015, respectively).

Conclusion: The results of this study indicated that the OCT and visual field findings showed good structure-function correlation. The N75-P100 amplitude and P100 latency of VEP was correlated with OCT and visual field parameters.

Keywords: Correlation; glaucoma; optical coherence tomography; visual evoked potentials; visual field.

Glaucoma is an optic neuropathy characterized by retinal ganglion cell (RGC) death and corresponding nerve fiber layer loss, which causes characteristic visual field (VF) loss and blindness. The number of people (aged between 40 and 80 years) with glaucoma was estimated to be 64.3 million in 2013, 76.0 million in 2020, and the number is predicted to be close to 111.8 million by 2040.[1]

Structural and functional changes to the visual system caused by glaucoma can be clinically measured with optical coherence tomography (OCT), VF, and visual evoked

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potential (VEP). Structural changes include loss of neuroretinal rim at the optic nerve head and thinning of the retinal nerve fiber layer (RNFL) which can be measured by OCT. Another parameter is the ganglion cell complex (GCC) which is formed by the RNFL, the ganglion cell layer, and the inner plexiform layer, corresponding to the axons, cell bodies, and dendrites of the RGCs. In detecting glaucoma, GCC thickness was reported to be superior to macular thickness.[2]

The loss of RGCs causes functional damage which can be measured by perimetry, seen as VF sensitivity loss.[3,4] Standard automated perimetry (SAP) is widely used in the evaluation of visual function and staging glaucoma progression.

As a non-invasive and objective diagnostic method, VEP is one of the tests that evaluate the visual function at the level of the occipital cortex with scalp electrodes. Glaucoma has been reported to affect the VEP by causing both reductions in amplitude and increases in latency. Increased pattern VEP latency has been associated with optic disc cupping and the presence of VF loss.[5,6] Full-field pattern reversal is the most used VEP stimulus because eyes are evaluated separately and it also focuses on the evaluation of the anterior segment of the visual pathways.

Determining progression is important for effective clinical management of patients with glaucoma, SAP is a functional but subjective test, VEP is another functional test with objective information. In monitoring progression, combining structural and functional tests will provide more reliable information and improve treatment. There are several studies that investigated the relation between structural and functional damage in primary open-angle glaucoma (POAG), but the results are still open to discussion. The aim of our study was to evaluate the correlation between functional (VF and VEP) and structural (OCT) tests in open-angle glaucoma patients.

Materials and Methods

This study was conducted in accordance with the Helsinki declaration. Ethics committee approval was not required; however, permission was obtained from the management of the Training and Research Hospital for this retrospective study.

This study included 56 eyes of 28 patients (15 women and 13 men) who were followed up with a diagnosis of POAG in the Department of Ophthalmology, Glaucoma Division in our clinic. The patients who met the inclusion criteria and had structural and functional tests completed within 6 weeks were selected from the hospital database. All subjects had bilateral and symmetric POAG and both eyes were included in the study.

The diagnosis criteria for open-angle glaucoma were normal appearance and open-angle on gonioscopy, intraocular pressure (IOP) >21 mmHg, characteristic glaucomatous optic nerve head change, and glaucomatous VF change. IOPs of all cases were under control with medical treatment (15.57±2.66 mmHg). The best-corrected visual acuity was above 0.6 in all cases according to the Snellen chart (decimal). Refractive errors were not greater than ±5 diopters spherical equivalent. The patients who had narrow or closed-angle in the gonioscopic examination, secondary glaucoma, a previous history of eye surgery, or other eye diseases (inflammatory eye disease, penetrating ocular trauma, senile macular disease, diabetic retinopathy, etc.) were excluded from the study.

All ophthalmological examinations including visual acuity, biomicroscopic anterior and posterior segment examination, IOP measurement with Goldmann applanation tonometry, and fundus examination were performed for all patients who were included in the study.

RNFL and GCC thicknesses were measured in all cases with RTVue-100 (Optovue, Inc., Fremont, CA) OCT device. Measurements with low signal strength (<50) and artifacts, focused outside the fovea or optic disc center were not evaluated. RNFL thickness was measured using 13 concentric ring scans, 1.3–4.9 mm in diameter (587–965 different axial scans per ring) centered on the optic disc. GCC was measured using the scan protocol "GCC." GCC was measured with 1 horizontal line with a 7 mm scan length (467 axial scans per line, centered 1 mm temporal to the fovea, and with a scan time of 0.59 s) and 15 vertical lines with a 7-mm scan length (400 axial scans per line, 0.5-mm interval between 2 lines, centered in the middle of the horizontal scan line). The average thicknesses of RNFL and GCC were examined.

A Roland-Consult Retiport device was used for VEP testing. For pattern VEP recording, the active electrode was placed 2 cm above the protuberensiya occipitalis externa in the occipital bone, while the reference electrode was placed on the vertex and the ground electrode on the forehead. While the patient was looking at the fixed point in the middle of the moving chessboard-shaped patterns on the screen 1 m in front of the room light, electrical potentials occurring in the occipital cortex were recorded. The patterns were recorded using two different size patterns; the pattern sizes used were 1° and 15 min. The contrast was 99% compared

to the Michelson constant. An average of 100 warnings in each pattern was taken. Records were repeated when the lid or peripheral artifacts exceeded 5%. The patient's focus on the fixation point was closely followed by an experienced electrophysiology technician. In addition to the patient's compliance with the test, behaviors that may affect the results such as pupil diameter, age, and refractive error were taken into account. In the pattern VEP measurements, the latency values of the N75 and P100 waves obtained for 1° and 15 min pattern were recorded in milliseconds (ms), and the amplitude values of the 1° and 15 min N75-P100 wave were recorded in microvolts (μV).

VF tests (24–2 central with fovea-on) were performed with a Humphrey standard automated perimeter (Humphrey-Zeiss Systems, Dublin, CA) using the Swedish Interactive Thresholding Algorithm standard protocol with stimulus size III and white object for all subjects. Tests with <20% fixation loss and false-positive and false-negative rates below 33% were regarded as reliable. The main indices of the Humphrey perimetry are mean deviation (MD) and pattern standard deviation (PSD). The VF index (VFI) is a global metric that is based mostly on pattern deviation.[7]

As defined by the Hodapp classification, an MD in the range of 0 to <−6 dB is a mild glaucomatous defect, in the range of −6−−12 dB is moderate, and >−12 dB is considered as a severe glaucomatous defect.

Statistical Analysis

In the presentation of descriptive statistics, the mean and standard deviation (mean ± SS) values were used. Statistical analysis was performed using SPSS Version 10.0 (SPSS Inc., Chicago, Illinois, USA). Data distribution was analyzed with the Kolmogorov-Smirnov test. Correlation analysis was evaluated by Pearson's correlation coefficient (r) in normally distributed data and by Spearman correlation coefficient (r) in non-normally distributed data and their statistical significance was evaluated. P<0.05 was considered to be statistically significant and p<0.001 was considered to be highly significant.

Results

Fifty-six eyes of 28 patients (15 women and 13 men) with a mean age of 57.61 (±10.54) years were included in the study. Table 1 summarizes the demographic characteristics of the patients included in the study.

Fifty-two eyes (92.85%) had mild glaucomatous defects (MD; −2.97±1.47) and 4 (7.14%) had moderate glaucomatous defects (MD; −7.01±1.17).

Table 1. Demographic characteristics and VEP, VF and OCT parameters

	Mean±Standard Deviation (Min/Max)
Age (years)	57.61±10.54 (18/71)
IOP (mmHg)	15.57±2.66 (10/22)
VFI (%)	96.16±3.63 (86/100)
MD (dB)	−3.26±1.79 (−8.60/−0.26)
PSD (dB)	2.45±1.26 (1.22/6.37)
RNFL (μm)	96.66±12.81 (62/132)
GCC (μm)	91.85±7.71 (70.97/106.52)
N75 (ms)	82.07±9.4 (60/90)
P100 (ms)	115.54±8.64 (90/130)
N75-P100 (μV)	8.61±5.80 (1.12/25.30)

IOP: Intraocular pressure; VFI: Visual field index; MD: Mean deviation; PSD: Pattern standard deviation; RNFL: Retinal nerve fiber layer; GCC: Ganglion cell complex; VEP: Visual evoked potential; VF: Visual field; OCT: Optical coherence tomography.

Table 2. Correlation analysis of VEP, VF analysis and RNFL and GCC thickness

	MD (dB)	PSD (dB)	VFI (%)
RNFL (μm)			
r	0.208	−0.324	0.237
P	0.125	0.015*2	0.79
GCC (μm)			
r	0.431	−0.264	0.253
p	0.001*1	0.049*2	0.06
N75 latency (ms)			
r	−0.048	−0.075	−0.65
p	0.725	0.58	0.636
P100 latency (ms)			
r	−0.037	0.173	−0.344
p	0.788	0.202	0.009*2
N75-P100 amplitude (μV)			
r	0.145	−0.195	0.127
p	0.285	0.15	0.353

[1]r: Pearson or [2]Spearman's correlation coefficient *p<0.05. VFI: Visual field index; MD: Mean deviation; PSD: Pattern standard deviation; VEP: Visual evoked potential; VF: Visual field; RNFL: Retinal nerve fiber layer; GCC: Ganglion cell complex.

VEP, VF, and OCT parameters are compared in Table 2. RNFL and PSD were negatively correlated (r=−0.324, p=0.015) (Fig. 1). GCC showed positive correlation with MD and negative correlation with PSD (r=0.431, p=0.001; r=−0.264, p=0.049, respectively) (Figs. 2 and 3). P100 latency and VFI were negatively correlated (r=−0.344, p=0.009) (Fig. 4).

The correlation of OCT parameters with VEP parameters is examined in Table 3. N75 latency was positively correlated with RNFL and GCC (r=0.375, p=0.004; r=0.324, p=0.015, respectively) (Figs. 5 and 6). RNFL was positively correlated with the amplitude of N75-P100 (r=0.586, p=0.000) (Fig. 7).

Table 3. Correlation analysis of VEPs and RNFL and GCC thickness parameters

	RNFL (µm)	GCC (µm)
N75 latency (ms)		
r	0.375	0.324
P	0.004*2	0.015*2
P100 latency (ms)		
r	−0.184	−0.258
p	0.174	0.055
N75-P100 amplitude (µV)		
r	0.586	0.228
p	0.000*2	0.090

[1]r: Pearson or [2]Spearman's correlation coefficient *p<0.05. VEP: Visual evoked potential; RNFL: Retinal nerve fiber layer; GCC: Ganglion cell complex.

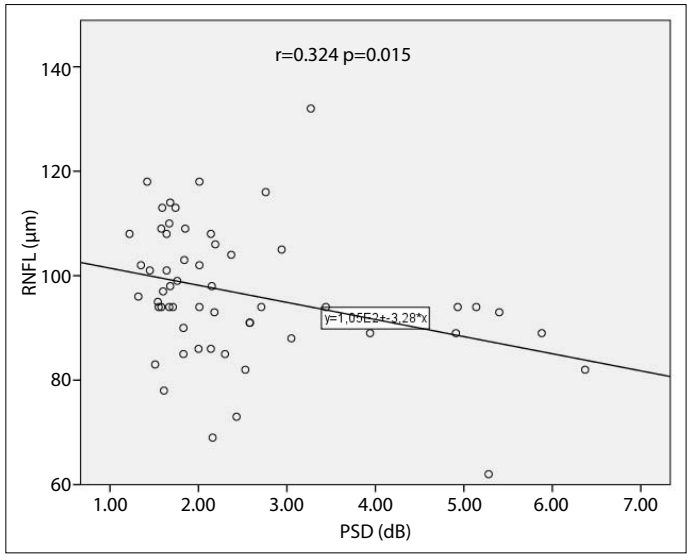

Fig. 1. Graphic representation of correlation analysis between RNFL thickness and PSD of the visual field. RNFL: Retinal nerve fiber layer; PSD: Pattern standard deviation.

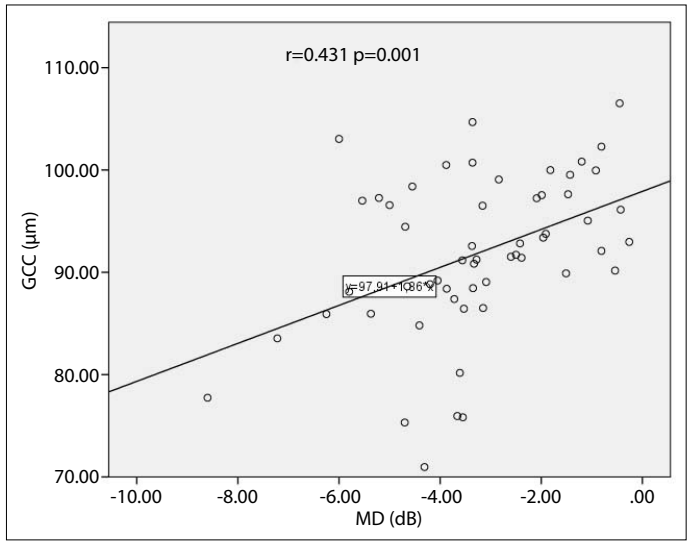

Fig. 2. Graphic representation of correlation analysis between GCC thickness and MD of the visual field. GCC: Ganglion cell complex; MD: Mean deviation.

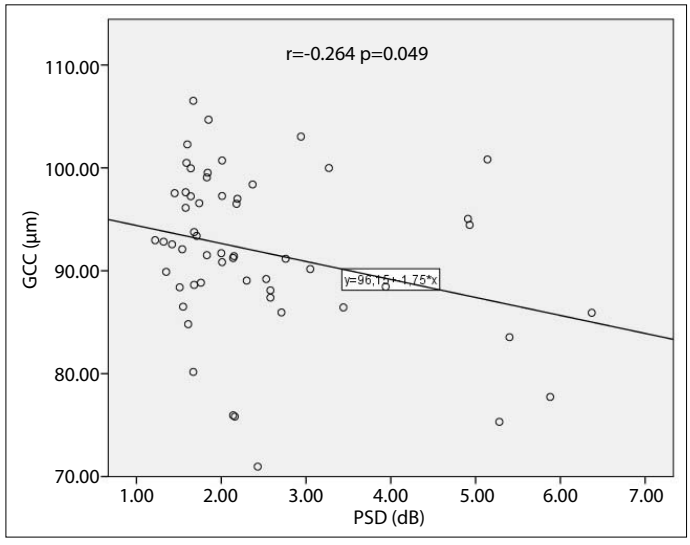

Fig. 3. Graphic representation of correlation analysis between GCC and PSD of the visual field. GCC: Ganglion cell complex; PSD: Pattern standard deviation.

Discussion

Glaucoma is an optic neuropathy condition characterized by progressive loss of RGCs and their axons. Neural damage can result in a loss of function and a decrease in vision-related quality of life. Detection of the progression is important in the evaluation of the risk of functional impairment, creating treatment strategies; to create these strategies structural and functional loss should be correlated and evaluated. Although several authors have recently studied the relationship between structural and functional tests in glaucoma, the results remain controversial.

The present study aimed to evaluate the correlation between VEP, RNFL, GCC, and VF in glaucoma patients.

A positive correlation between MD and GCC was observed in the current study. However, the correlation between MD and RNFL was not statistically significant. In their study, Kita et al.[8] found a strong relationship between MD and temporal RNFL. In a recent study, MD showed a strong correlation with average RNFL and moderate correlation with GCC parameters.[9] Similarly, there are several studies that showed a moderate correlation between MD and RNFL parameters.[10–15] A moderate relationship between MD and GCC parameters was also reported in several other studies.[8,11–14] Our study observed significant correlations between RNFL and GCC thickness with PSD in the negative direction. It can be concluded that GCC has a stronger relationship with VF than RNFL, according to its correlation

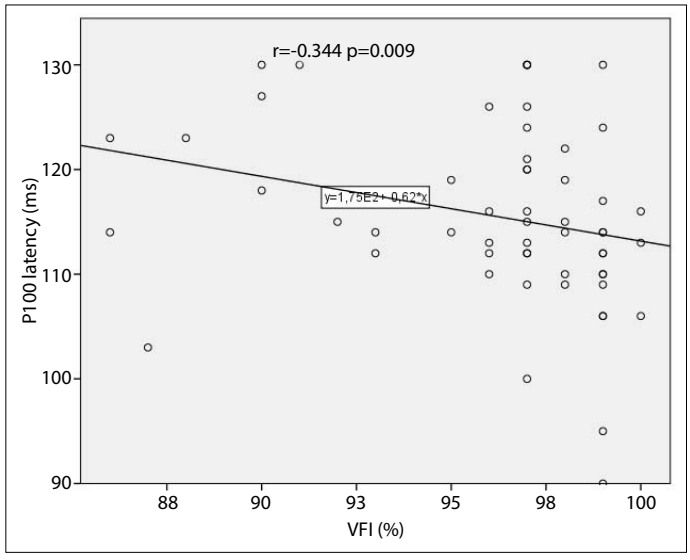

Fig. 4. Graphic representation of correlation analysis between P100 latency of VEP and VFI of the VF. VEP: Visual evoked potential; VFI: Visual field index; VF: Visual field.

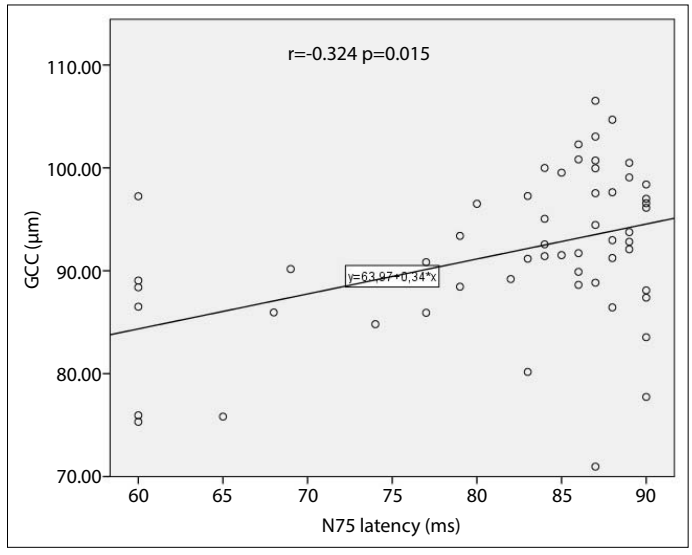

Fig. 6. Graphic representation of correlation analysis between N75 latency of VEP and GCC thickness. VEP: Visual evoked potential; GCC: Ganglion cell complex.

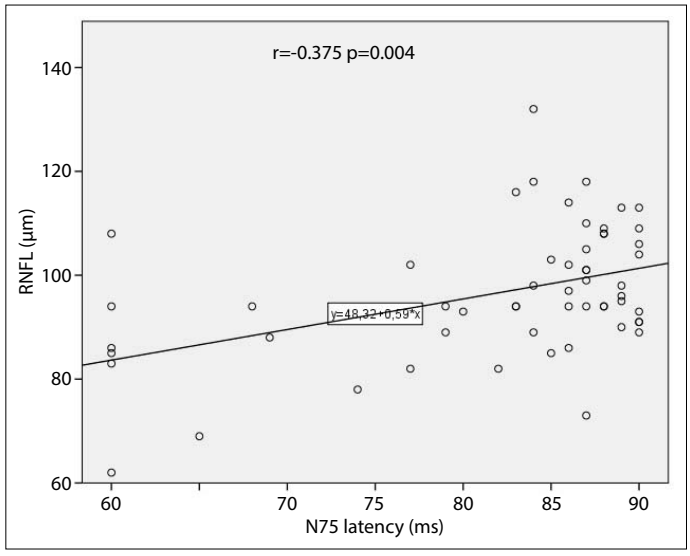

Fig. 5. Graphic representation of correlation analysis between N75 latency of VEP and RNFL thickness. VEP: Visual evoked potential, RNFL: Retinal nerve fiber layer.

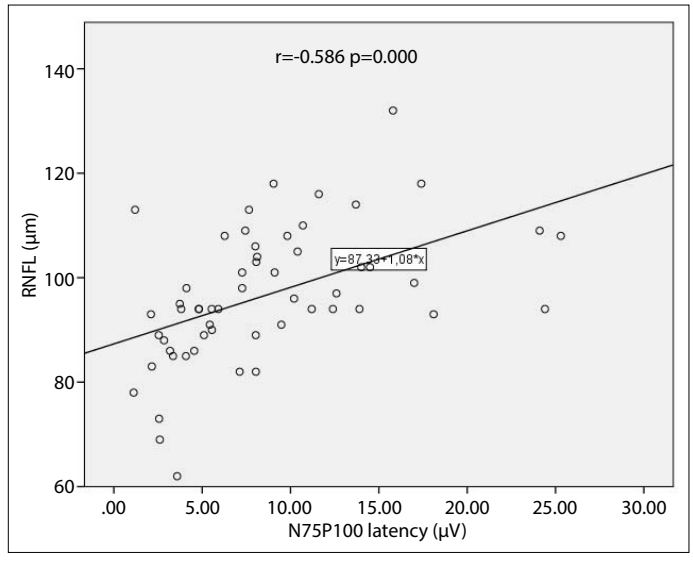

Fig. 7. Graphic representation of correlation analysis between N75-P100 amplitude of VEP and RNFL thickness. VEP: Visual evoked potential; RNFL: Retinal nerve fiber layer.

with both MD and PSD. The relationship between PSD and average RNFL was evaluated in several studies, showing a moderate-to-strong relationship.[9,12,14,15] In the same manner, a moderate-to-strong relationship was reported between GCC parameters and PSD.[12,14,16] In their study, Iutaka et al.[17] reported a weak, but statistically significant, positive correlation between VFI and RNFL parameters. In the present study, no correlations were observed between VFI and OCT parameters.

The correlation between VEP and VF parameters was evaluated in several studies. Ruchi et al.[18] found that there was a negative correlation between MD values and P100 latency, and these parameters were also correlated by Horn.[19] In their study, Parisi also reported that the latency of P100 in POAG was significantly prolonged compared to the control group, and there was a significant correlation with modifications of MD.[20] According to Towle et al.,[21] there was a significant correlation between increased pattern VEP latency, Humphrey perimetry defects, and funduscopic aspect of the optic disc in POAG patients. In a recent study, the MD values of POAG patients were positively correlated with the amplitude, while negatively correlated with the latency of P100.[22] Parisi et al.[23] showed a highly significant positive correlation between P100 amplitude and HFA 24/2

MD. Also, the MD values in their POAG patients were negatively correlated with the latency of P100. Kothari et al.[24] investigated the correlation of VEP responses in POAG patients with PSD of their Humphrey VF; they reported a highly significant negative correlation of P100 amplitude, along with a statistically significant positive correlation of N70 latency, P100 latency, and N155 latency. In our study, the correlation between VEP and VF parameters did not reach statistical significance; there was only a negative correlation between latency of P100 and VFI. To our knowledge, there are no studies that identify the correlation between VFI and VEP parameters.

With that being stated, there are few studies that investigated the correlation between VEP and OCT parameters in POAG. Parisi et al.[25] evaluated the correlations between OCT, pattern electroretinogram, and VEP in POAG patients, where VEP parameters showed a significant delay in implicit time and a reduction in amplitude. No correlations were found between RNFL values and VEP parameters. In their study, Avinash et al.[26] assessed the relationship between RNFL and VEP in early POAG; despite there being highly statistically significant differences between the VEP measurements of the glaucoma group compared to the control group, the average RNFL thickness and VEP responses were not statistically correlated. In the present study, RNFL thickness was positively correlated with the amplitude of N75-P100.

Unexpectedly, a positive correlation between OCT parameters and latency of N75 was observed in our study. N75 wave, which is the early component of VEP, is formed by activation of the striate cortex in the primary visual area and may be affected by individual differences in the position and size of the striate cortex. Therefore, N75 latency is not generally used clinically, and it could be affected by numerous factors, such as age, gender, eye dominance, eye movement, visual acuity, pattern luminance, VF, and pupillary diameter. However, the P100 wave, which is the late component of VEP, occurs by activation of the extrastriate cortex and almost never changes with age and position. Therefore, it was concluded that P100 latency prolongation is the most reliable indicator of a clinically significant abnormality, as it is least affected by technical factors and the degree of patient cooperation.[27,28] In the current study, P100 latency was correlated with VFI. In addition to P100 latency, N75-P100 amplitude indicated a high level of reliability in their correlation with RNFL thickness. Unlike P100 latency and N75-P100 amplitude, N75 latency was not correlated with structural tests and VF; therefore, it cannot be assessed as a parameter in glaucoma progression. The correlations observed in the study indicate that VF and OCT are comparable in detecting glaucoma progression.

The main limitation of this study was that it is a retrospective study. In addition, it consists of mostly mild glaucoma patients and small numbers of moderate glaucoma patients, and there were no advanced glaucoma patients. It was reported that glaucoma progression and advanced glaucoma affect VEP results.[18] Therefore, further studies including patients with more advanced glaucoma, along with a larger number of patients, are necessary to corroborate these results. Another limitation of the study is the lack of a control group.

Conclusion

Diagnosis of glaucoma involves a combination of detecting structural damage and functional defects. Therefore, using VF, OCT, and VEP in a complementary way could be useful in monitoring glaucoma progression. However, patients with unreliable or questionable VFs can be evaluated with VEP responses.

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Conflict of Interest: None declared.

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