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Structural changes of macula and optic disk of the fellow eye in patients with nonarteritic anterior ischemic optic neuropathy

R. Duman · G. F. Yavas · I. Veliyev · M. Dogan · R. Duman

Abstract

Purpose The aim was to assess the ganglion cell complex (GCC) thickness, retinal nerve fiber layer (RNFL) thickness and optic disk features in the affected eyes (AE) and unaffected fellow eyes (FE) of subjects with unilateral nonarteritic anterior ischemic optic neuropathy (NAION) and to compare with healthy control eyes (CE) using spectral domain-optical coherence tomography (SD-OCT).

Methods This study included 28 patients and age, sex and refraction-matched 28 control subjects. Mean GCC thickness and peripapillary RNFL thickness in four quadrants measured by cirrus SD-OCT were evaluated in both AE and FE of patients and CE. In addition, optic disk measurements obtained with OCT were evaluated.

Results Mean GCC thickness was significantly lower in AE compared with both FE and CE ($P < 0.001$), and mean GCC thickness in FE was significantly lower than CE ($P = 0.022$). In addition, mean RNFL thickness in superior and nasal quadrants significantly decreased in FE compared with CE ($P = 0.020$ and 0.010, respectively). Furthermore, AE had significantly greater optic disk cupping compared with both FE and CE ($P < 0.001$).

Conclusions GCC and RNFL thickness decreased significantly at late stages of NAION, in both AE and FE compared with CE, suggesting that some subclinical structural changes may occur in FE despite lack of obvious visual symptoms. In addition, there was no significant difference in optic disk features between the CE and FE. And significantly greater optic disk cupping in the AE compared with both FE and CE supports the acquired enlargement of cupping after the onset of NAION.

Keywords Unilateral nonarteritic anterior ischemic optic neuropathy · Optical coherence tomography · Fellow eye · Ganglion cell complex · Retinal nerve fiber layer

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Introduction

Nonarteritic anterior ischemic optic neuropathy (NAION) is one of the major cause of blindness in people aged over 50 years. The incidence of NAION ranges between 2.3 to 82/100.000 in various studies

[1, 2]. NAION is a multifactorial disease where systemic diseases including diabetes mellitus, hypertension/hypotension, atherosclerosis, cardiovascular disorders or a migraine and local risk factors, such as poor optic nerve head blood supply, vasospasm, raised intraocular pressure or defective autoregulation, may play an etiopathogenetic role [3, 4]. However, the exact pathophysiological mechanisms underlining NAION are still unknown.

Although NAION starts unilaterally in the majority of cases, it has been reported that the fellow eyes (FE) may be involved in 15–25% of patients within 3–5 years [5, 6]. However, the study findings focusing on unaffected FE are quite limited, and to the best of our knowledge, previously no study reported subclinical retinal changes in the unaffected FE compared with healthy control. Similarly, which cases are under the risk of FE involvement needs to be clarified.

It is known that evaluation of peripapillary retinal nerve fiber layer (RNFL) and ganglion cell complex (GCC) by spectral domain-optical coherence tomography (SD-OCT), at least 6 months after the acute event, is a sensitive method correlating with final visual acuity or visual field mean deviation in NAION [7, 8]. The purpose of this study was to assess the GCC thickness, RNFL thickness and optic nerve head features in the affected eyes (AE) and FE of subjects with unilateral NAION and to compare the results with healthy controls using SD-OCT.

Materials and methods

This cross-sectional analytic study included 28 patients with unilateral NAION and age-, sex- and refraction-matched 28 subjects without any ocular abnormality including media opacities, glaucoma or any other retinal pathology. Right eyes of control subjects were evaluated as a control group. This study was given institutional review board approval and was conducted in accordance with the tenets of the Declaration of Helsinki. The database at our department of ophthalmology clinic (School of Medicine, Afyon Kocatepe University, Afyonkarahisar, Turkey) was used to search all cases of NAION between January 1, 2014, and January 1, 2017. Patients having lack of data, poor image analysis, optic disk edema or reattack were excluded from the study. The presence of any systemic disorder including diabetes mellitus,

hypertension/hypotension or cardiovascular disease was noted. Best-corrected visual acuity was recorded by Snellen chart. Refractive error examination was performed with an autorefractometer. OCT scanning was performed with Cirrus SD-OCT (Carl Zeiss Meditec, Dublin, CA, USA). Peripapillary RNFL thickness in temporal (RNFLT), superior (RNFLS), nasal (RNFLN) and inferior (RNFLI) quadrants and mean GCC (Macular ganglion cell layer plus inner plexiform layer) thickness were evaluated with SD-OCT at least 6 months after presentation in AE, FE and control eyes (CE) (Figs. 1, 2). Optic nerve head measurements were taken with SD-OCT via automated optic disk analysis protocol, and disk area, cup area and rim area were recorded.

The statistical analysis was performed with SPSS software version 18.0 (SPSS Inc, Chicago, IL). Continuous variables were presented as a mean ± standard deviation. Comparisons between the FE and AE of patients with NAION were performed by the Wilcoxon signed-rank test. And the Mann–Whitney U test was used to compare the FE/AE and the CE.

Results

The study included 28 patients and age-, sex-, and refraction-matched 28 control subjects. The mean age was 62.1 years (50–80) in the patient group and 59.9 years (43–79) in the control group ($P = 0.95$). Female/male distribution in groups was similar (11/17 in the patient group vs. 10/18 in the control group, $P = 0.93$). Two patients had diabetes mellitus, 7 patients had hypertension and 1 patient had anemia in unilateral NAION group, whereas 5 subjects had diabetes mellitus and 10 subjects had hypertension in the control group.

Mean visual acuity was 0.57 ± 0.40 LogMAR units in the AE, 0.01 ± 0.02 LogMAR units in the unaffected FE and 0.01 ± 0.03 LogMAR units in the CE.

Mean GCC thickness was 53.1 ± 14.6 μm in AE, 74.5 ± 18.4 μm in FE and 83.4 ± 6.6 μm in the CE. Mean GCC thickness was significantly lower in AE compared with unaffected FE and CE ($P < 0.001$). Furthermore, mean GCC thickness in FE was significantly lower than CE ($P = 0.022$).

Mean RNFLI/RNFLS thickness significantly decreased in AE compared with FE (RNFLI:

Fig. 1 Optical coherence tomographic images showing the RNFL thickness profile of the NAION eye and fellow eye in temporal, superior, nasal and inferior quadrants
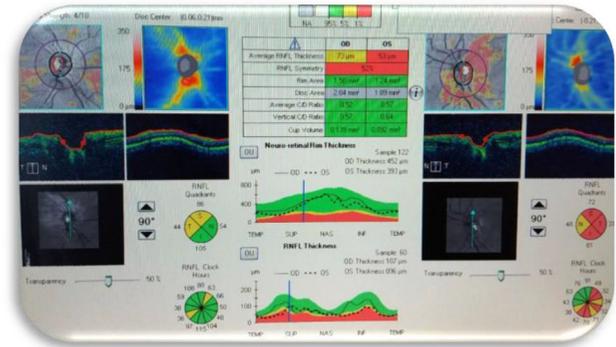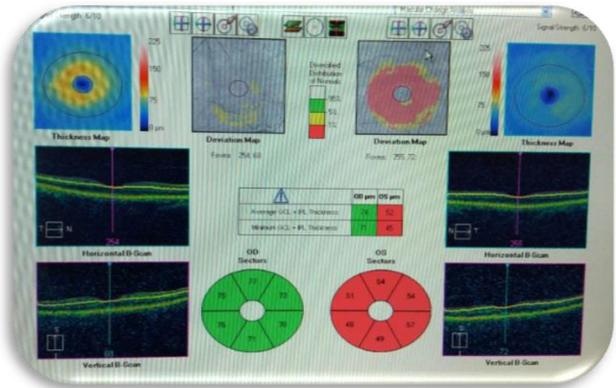

Fig. 2 Optical coherence tomographic images through the foveal center showing the GCC profile of the NAION eye (red color) and fellow eye (yellow color)

81.9 ± 43 vs. 108.0 ± 28.3 μm, $P = 0.004$; RNFLS: 66.8 ± 44.0 vs. 99.3 ± 31.9 μm, $P = 0.002$, respectively), whereas there was no significant difference in RNFLT and RNFLN thickness ($P = 0.207$ and 0.099, respectively). In addition, mean RNFLS and RNFLN thickness significantly decreased in FE compared with CE ($P = 0.020$ and 0.010, respectively). Comparative study findings including mean peripapillary RNFL and GCC thickness parameters are summarized in Table 1.

The mean optic disk area was significantly smaller and the mean cup area was significantly greater in the AE compared with CE ($P = 0.036$ and < 0.001, respectively), despite no significant differences between FE and CE ($P = 0.066$ and 0.090, respectively). Optic disk measurements in groups are given in Table 2.

Discussion

NAION is a multifactorial ocular disease causing blindness with an unknown etiopathogenesis. In most cases, it presents unilaterally with significant vision loss in AE although FE involvement may occur in following years in some patients [5, 6]. Majority of previous studies on unilateral NAION has focused on imaging findings of AE; however, data about unaffected FE compared with healthy controls are limited. In recent years, SD-OCT has been increasingly important in the diagnosis and follow-up of NAION. In particular, evaluating GCC and RNFL thickness is a sensitive method correlating with final visual defects [7, 9–14]. In early phases of NAION, optic disk edema is present which may cause some diagnostic difficulties in diagnosis of early axonal damage. Thus, some studies reported that OCT is most useful at 6 months after onset of NAION when RNFL loss has reached a plateau [13]. So in this study, we evaluated OCT findings at 6 months of presentation, and we mainly aimed to focus on unaffected FE in unilateral NAION cases compared with healthy CE by measuring GCC and peripapillary RNFL thickness by SD-OCT.

Various studies showed significant thinning in GCIPL and RNFL in the AE compared with FE and

Table 1 Comparison of visual acuity, ganglion cell complex thickness and retinal nerve fiber layer thickness between affected eyes, unaffected fellow eyes and healthy control eyes

Parameter	AE	FE	CE	P value$^+$ (AE vs. CE)	P value$^+$ (FE vs. CE)	P value^{++} (AE vs. FE)
Mean VA (logMAR)	0.57 ± 0.40	0.01 ± 0.02	0.0 1 ± 0.03	< 0.001*	0.642	< 0.001*
Mean GCC (μm)	53.1 ± 14.6	74.5 ± 18.4	83.4 ± 6.6	< 0.001*	0.022*	< 0.001*
Mean RNFLS (μm)	66.8 ± 44.0	99.3 ± 31.9	118.2 ± 15.2	< 0.001*	0.020*	0.002*
Mean RNFN (μm)	56.6 ± 29.2	63.7 ± 17.1	71.9 ± 14.0	< 0.001*	0.010*	0.099
Mean RNFLI (μm)	81.9 ± 43.1	108 ± 28.3	60.6 ± 14.8	< 0.001*	0.337	0.004*
Mean RNFLT (μm)	54 ± 18.1	60.6 ± 14.8	65.1 ± 14.4	0.012*	0.436	0.207

AE affected eyes, *FE* fellow eyes, *CE* control eyes, *VA* visual acuity, *GCC* Ganglion cell complex, *RNFLT* temporal quadrant retinal nerve fiber layer, *RNFLS* superior quadrant retinal nerve fiber layer, *RNFLI* inferior quadrant retinal nerve fiber layer, *RNFLN* nasal quadrant retinal nerve fiber layer

*Statistical significance

$^+$Comparison between groups with Mann–Whitney *U* test

$^{++}$Comparison between groups with Wilcoxon signed-rank test

Table 2 Comparison of optic disk parameters between affected eyes, unaffected fellow eyes, and control eyes

Parameters	AE	CE	FE	P value$^+$ (AE vs. CE)	P value$^+$ (FE vs. CE)	P value^{++} (AE vs. FE)
Mean disk area ± SD (mm^2)	2.20 ± 0.55	2.50 ± 0.34	2.30 ± 0.45	0.036*	0.066	0.082
Cup Area ± SD (mm^2)	1.40 ± 0.51	0,61 ± 0.33	0,70 ± 0.36	< 0.001*	0.09	< 0.001*
Rim Area ± SD (mm^2)	0.8 ± 0.30	1.89 ± 0.39	1.60 ± 0.39	< 0.001*	0.061	< 0.001*

AE affected eyes, *FE* fellow eyes, *CE* control eyes

*Statistical significance

$^+$Comparison between groups with Mann–Whitney *U* test

$^{++}$Comparison between groups with Wilcoxon signed-rank test

CE, which were consistent with our study findings [11, 12].

The literature data on a comparison between FE and CE are limited. Saito et al. [13] and Dağ et al. [14] found no significant difference between the FE of patients with unilateral NAION and the control group in terms of RNFL thickness. However, they did not evaluate GCC thickness, which may be more sensitive than RNFL in detecting early axonal damage in NAION, as previously reported in some studies [9]. Furthermore, they did not report time of presentation at imaging. In contrast to their study, we also evaluated GCC thickness and found that mean RNFLS, RNFLN and GCC thickness significantly decreased in FE compared with CE at 6 months of presentation. With the present study findings, we suggest that early changes especially in GCC and nerve fiber layer of the superior and nasal quadrant may occur in FE despite lack of obvious visual symptoms. Thus, being aware of this risk may help in close follow-up of FE in patients with unilateral NAION and reducing final visual defects. Similarly, some previous studies reported some structural abnormalities in bilateral eyes of unilateral NAION cases, which can also

support our study findings [14]. Time after disease onset may influence imaging outcomes in NAION, so studies performing imaging at different times of presentation may cause conflicting results. According to our study findings, we suggest performing imaging also at 6 months of presentation.

Previously several studies comparing optic disk parameters in patients with NAION reported controversial results. The morphologic changes that occur after NAION and predisposing characteristics of the optic disk before the formation of NAION still need to be clarified. Danesh-Meyer et al. [15] reported a slight but significantly greater cup-to-disk ratio in AE of NAION using the Heidelberg retina tomograph, despite no significant difference in the cup area. Contreras et al. [16] found no significant difference in the optic disk area among the CE, NAION-AE and NAION-FE by using the optic nerve head analysis protocol of the StratusOCT. Doro and Lessell [17] and Beck et al. [18] found a smaller cup-to-disk area ratio in FE compared with CE. Saito et al. [13] reported that the cup was slightly larger in AE compared with FE, suggesting the acquired enlargement of the cupping after NAION develops. In the same study, comparison of FE and CE suggested a smaller disk area and smaller cupping were predisposing factors for the development of NAION. Similarly, in the present study, we showed significantly greater cupping in AE compared with both FE and CE. This finding supports the acquired enlargement of the cupping after the development of NAION. However, in contrast to the study findings by Saito et al. [13], we found no statistically significant difference between FE and CE, despite slightly greater cupping and smaller disk area in FE. This discrepancy between different studies may be associated with several factors such as the use of different techniques and analysis protocols, lack of age or refraction matching in some studies, a different number of subjects, different examiners and the time of measurements after the onset of NAION.

The present study had some limitations. In our study, the imaging findings at 6 months of presentation were evaluated. Larger prospective studies with longer follow-up periods may be needed to evaluate final GCC and RNFL outcomes in AE and FE. And comparing FE findings at both disease onset and at 6 months of presentation would be more useful, which could not be obtained because of technical reasons. In addition, it would be more informative if the visual function could also be assessed with more tests such as perimetry, contrast sensitivity and color vision test.

In conclusion, the thickness of GCC and RNFL decreased significantly at late stages of NAION, in both AE and FE compared with CE. In addition, AE had greater cupping and smaller disk area compared with both FE and CE, suggesting acquired enlargement of cupping after the onset of NAION. Despite lack of obvious visual symptoms in FE, it should be kept in mind that some early structural changes may occur also in FE, and measurement of GCC, RNFLS and RNFLN thickness may give clue about further outcomes. Why RNFL thinning starts firstly in the superior and nasal quadrants and which local factors play role in these results needs to be further clarified.

Compliance with Ethical Standards

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

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional research committee (Ethics Committee of Afyon Kocatepe University, School of Medicine, Afyonkarahisar, Turkey) and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

Informed consent Informed consent was obtained from the patients included in this study.

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