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To cite this article: Mei Han, Chen Zhao, Quan-Hong Han, Shiyong Xie & Yan Li (2016) Change of Retinal Nerve Layer Thickness in Non-Arteritic Anterior Ischemic Optic Neuropathy Revealed by Fourier Domain Optical Coherence Tomography, Current Eye Research, 41:8, 1076-1081, DOI: 10.3109/02713683.2015.1084640

To link to this article: http://dx.doi.org/10.3109/02713683.2015.1084640

Published online: 18 Nov 2015.

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Change of Retinal Nerve Layer Thickness in Non-Arteritic Anterior Ischemic Optic Neuropathy Revealed by Fourier Domain Optical Coherence Tomography

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ABSTRACT
Purpose: To examine the changes of non-arteritic anterior ischemic optic neuropathy (NAION) by serial morphometry using Fourier domain optical coherence tomography (FD-OCT).

Materials and methods: Retrospective study in patients with newly diagnosed NAION (n=33, all unilateral) and controls (n=75 unilateral NAION patients with full contralateral eye vision) who underwent FD-OCT of the optic disk, optic nerve head (ONH), and macula within 1 week of onset and again 1, 3, 6, and 12 months later. The patients showed no improvement in vision during follow-up.

Results: Within 1 week of onset, all NAION eyes exhibited severe ONH fiber crowding and peripapillary retinal nerve fiber layer (RNFL) edema. Four had subretinal fluid accumulation and 12 had posterior vitreous detachment (PVD) at the optic disc surface. Ganglion cell complex (GCC) and RNFL thicknesses were reduced at 1 and 3 months (p < 0.05), with no deterioration thereafter. Initial RNFL/GCC contraction magnitude in the superior hemisphere correlated with the severity of inferior visual field deficits. Conclusions: NAION progression is characterized by an initial phase of accelerated RNFL and GCC deterioration. These results reveal that the kinetic change of neural retina in NAION and may have implication on the time window for treatment of NAION. FD-OCT is useful in the evaluation of NAION.

Introduction

Non-arteritic anterior ischemic optic neuropathy (NAION) is one of the most frequent causes of permanent partial blindness in the middle-aged and elderly population. Patients experience sudden painless vision loss, optic disc edema, and visual field (VF) defects resulting from damage to the prelaminar region of the optic nerve. VF examination may reveal focal defects or pervasive vision loss depending on the extent of optic nerve damage. Pathological scotomas are often associated with arc-shaped regions of vision loss. Studies performed with the Heidelberg Retina Tomograph (HRT; Heidelberg Engineering, Heidelberg, Germany) have confirmed the presence of a smaller optic nerve head (ONH) with “fiber crowding” in NAION patients. While ONH changes in NAION patients have been evaluated by Stratus optical coherence tomography (Carl Zeiss Meditec, Dublin, CA), to our knowledge, seldom studies have directly analyzed morphological changes of the retinal nerve fiber layer (RNFL) and ganglion cell complex (GCC) in NAION patients. The poorly described pathological and morphological progression of NAION is undoubtedly a significant impediment to optimal treatment.

Fourier domain optical coherence tomography (FD-OCT) yields high-resolution three-dimensional information on retinal structure, including RNFL thickness, GCC thickness, and the spatial relationship between the retina and vitreous body, by rapidly acquiring reflective measurements through the optical axis. A previous study showed that FD-OCT was a good modality to detect ganglion cell loss in patients with NAION. The aim of the present retrospective study was to analyze the morphological characteristics of the optic nerve head (ONH) and macula in patients with NAION by FD-OCT imaging. RNFL thickness, GCC thickness, and vitreous body characteristics were examined during the year following onset to assess the value of sequential FD-OCT monitoring for analysis of morphologic changes.

Materials and methods

Patients

Thirty-three NAION patients (14 males and 19 females, 50–73 years, mean, 55.6 ± 5.2 years) diagnosed at the Department of Ocular Fundus Disease, Tianjin Eye Hospital, from December 2008 to May 2011 were included in this retrospective study. Diagnosis of NAION was made on the basis of comprehensive opthalmologic examination including detailed history, visual acuity assessment with the Snellen chart, optic nerve function tests, fundus examination, stereoscopic color fundus photography, and FD-OCT scanning of the ONH and macula. Some patients were also diagnosed using fluorescein angiography. Diagnostic criteria for NAION were (1) sudden and painless vision loss; (2) acute optic disc edema with or without hemorrhage at the optic disc rim as observed by fundoscopy;
(3) positive relative afferent pupillary defect (RAPD); and (4) specific VF defects including arc-shaped defects, and quadrant defects. All patients included in the present study showed no improvement in vision for 12 months after diagnosis. Criteria for exclusion were (1) arteritic AION diagnosed based on clinical and laboratory findings; or (2) other diseases that may be associated with optic disc edema. The study protocol adhered to the tenets of the Declaration of Helsinki. The Tianjin Eye Hospital Institutional Review Board approved the study protocol, and the need for individual consent was waived by the committee.

Seventy-five control subjects (30 males and 45 females, 50–73 years, 56.68 ± 6.23 years) with a history of unilateral NAION were included for the same examinations of the unaffected eye. All unaffected eyes had 20/20 vision and had normal VF. All control and study eyes were from different patients. Controls underwent FD-OCT scanning only.

**Treatment and follow-up**

All the patients were evaluated within 1 week of symptom onset. Other causes of optic neuropathy were ruled out by clinical follow-up and additional testing, including erythrocyte sedimentation rates, temporal artery biopsies, or neuroimaging, as indicated. Detailed history, visual acuity assessment with the Snellen chart, optic nerve function tests, fundus examination, stereoscopic color fundus photography, and FD-OCT scanning of the ONH and macula were performed at 1 week and at 1, 3, 6, and 12 months after presentation. Patients demonstrated no improvements in visual status during the follow-up period (1-week vision: 0.61 ± 0.38; 1-month vision: 0.60 ± 0.36; 3-month vision: 0.56 ± 0.38; 6-month vision: 0.64 ± 0.35; 12-month vision: 0.51 ± 0.34; all p > 0.05). The control subjects received only a FD-OCT scanning of the ONH and macula.

Patients received IV injections of 800 mg/d of deproteinized calf blood extracts, and IM injections of vitamins B1 and B12 once a day. This is based on the possibility that NAION is caused by cardiovascular risk factors such as high levels of homocysteine and Lp(a) and low levels of vitamins B.<sup>9,10</sup> Vitamin B12 was given in order to decrease homocysteine levels.<sup>11,12</sup> As for deproteinized calf blood extracts, it was to limit neurological damage or deterioration.<sup>13</sup>

**FD-OCT acquisition and analysis**

FD-OCT images (RTVue; Optovue, Inc., Fremont, CA) were generated using standard scans, 6 mm in axial depth, 6 mm in the transverse direction, and with an axial resolution of 5 μm. Each planar image was 1024 axial × 1024 transverse pixels. Circumferential scans of a radius of 3.4 mm were used for RNFL imaging. Sectional scans of the optic disc as well as horizontal and sectional scans of the macula were also obtained. Planar or circumferential imaging yielded a map of RNFL thickness, a topographic map of the optic disc, and a map of ganglion cells at the macula. High-quality scans (signal score of 4 or higher) were saved as soon as they were acquired. The morphological features of the images were analyzed and quantified. The ganglion cell complex includes the axons of the nerve fiber layer, the cell bodies in the ganglion cell layer, and dendrites in the inner plexiform layer. All morphometric parameters were calculated by the FD-OCT software (Optovue Meditec, Fremont, CA) except neurosensory retinal layer thickness (NRLT). The system allows the measurements for thickness only. The GCC thicknesses, GCC parameters, RNFL thicknesses, and disc parameters were assessed automatically using the GCC and ONH map. The GCC was measured using the scan protocol “GCC”. This protocol covers a 7 × 7 mm rectangular area of the macula, centered 0.75 mm temporal to the fovea.<sup>8</sup> The “ONH” protocol was used to evaluate the NFL thicknesses and the disc parameters. This protocol generates a map of the NFL thicknesses, based on measurements obtained along a circle 3.40 mm in diameter, centered on the optic disc. NRLT was obtained by manual measurement in the macular analysis. Topographic map analysis was automatically created by the software. NRLT refers to the neuroepithelial thickness in fovea centralis and is measured by drawing a perpendicular line from the lowest point of the neuroepithelial fovea to the retinal pigment epithelium.

VF assessment was performed using a Humphrey Field Analyzer II (Humphrey-Zeiss Instruments, San Leandro, CA) and the SITA-Fast Central 24-2 Threshold Test program.

**Statistical analysis**

Statistical analysis was performed using SPSS 11.5 (SPSS Inc., Chicago, IL). Data are presented as means ± standard deviation (SD). Morphometric means were compared by one-factor analysis of variance (ANOVA). Coefficients of determination from correlation analysis were used to evaluate the relationships among RNFL, GCC, and VF. p < 0.05 was considered statistically significant.

**Results**

All newly diagnosed NAION patients included in this study had unilateral acute loss of visual acuity and VF defects suggestive of RNFL and GCC damage, including arcuate and (or) altitudinal VF loss, and all had relative afferent pupillary defects (RAPD). Best corrected visual acuity (BCVA) in the NAION group ranged from "only able to count fingers" to 20/20. Sixteen patients had systemic diseases including diabetes (five patients), hypertension (10 patients), and heart disease (one patient). At 1 week or less after onset, color fundus photography revealed diffuse swelling of the optic disc in 18 eyes, segmental swelling within the optic disc in 15 eyes, and a blurred optic disc border in all 33 eyes. The optic disc color was normal or slightly pale, which might be indicative of congestion by peripapillary hemorrhages (Figure 1A). At the 1-month examination and all examinations thereafter, signs of optic nerve atrophy were observed, as well as a pale optic disc with a clear border, thinning of the peripapillary arteries, and visible foveolar reflection (Figure 2A). Nineteen (57.6%) patients had inferior VF defect, two had superior hemifields VF defect, four had nasal side VF defect, three temporal VF defect, three had diffuse VF defect, one had concentric
contraction, and one patient was excluded because the test could not be performed. The average VF MD and PSD were detected as 17.44 ± 5.82 decibels (dB) and 10.58 ± 1.44 dB, respectively. The thickness of superior hemisphere RNFL and GCC rapidly decreased and correlated with inferior VF defect ($r = 0.233, r = 0.262, p < 0.05$).

On FD-OCT images within 1 week post-onset, five eyes exhibited diffuse optic disc swelling with almost no remaining physiologic cup (Figure 1B), 25 eyes had diffuse optic disc swelling with narrowing of the physiologic cup, and three eyes exhibited optic disc swelling restricted to the nasal side (two eyes) or the superior aspect (one eye) of the optic disc. Partial posterior vitreous detachment (PVD) and traction at the surface of the optic disc was observed in 12 eyes. Eleven eyes exhibited a thickened retinal neurosensorial layer extending from the optic disc to the macula, and four showed edema of the neurosensorial layer from optic disc to macula, with subfoveal fluid and peripapillary subretinal hyporeflectivity adjacent to an elevated ONH resembling central serous maculopathy (Figure 1B). Fluorescein angiograms were available for these 15 patients and showed staining of the optic disc but no accumulation of dye in or around the macula. In the other 18 eyes, the reflections from the neurosensorial retinal layer and retinal pigment epithelial (RPE) layer were normal. By 1 month after onset, the optic disc swelling and subretinal fluid accumulation had resolved, but optic nerve atrophy was evident in all patients. The 1-month FD-OCT measurements showed reductions in RNFL and GCC thickness in all patients, and 22 eyes showed PVD at the surface of the optic disc (Figure 2B).

Comparative demographic data and morphometric results obtained by FD-OCT from new NAION patients and the control group are detailed in Table 1 and Figure 3. Age was similar in the two groups ($p = 0.493$), but there were significant differences in average NRLT at the foveal region, optic disc area, nerve head volume (NHV), cup area, and cup-to-disc (C/D) area ratio between groups. Mean NRLT at the foveal region, optic disc area, and NHV were at their highest level within 1 week of onset in new NAION patients and significantly higher than in the control group ($p < 0.05$) at this time, but decreased to control values thereafter (Table 1).

**Table 1.** Comparison of FD-OCT parameters between the NAION group at 1 week and the control group (mean ± SD).

<table>
<thead>
<tr>
<th>Parameter</th>
<th>NAION (n = 33)</th>
<th>Control (n = 75)</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>55.6 ± 5.2</td>
<td>56.7 ± 6.2</td>
<td>0.376</td>
</tr>
<tr>
<td>Gender (male:female)</td>
<td>14:19</td>
<td>30:45</td>
<td>0.813</td>
</tr>
<tr>
<td>NRLT at fovea (µm)</td>
<td>180.24 ± 52.31</td>
<td>162.26 ± 17.34</td>
<td>0.011</td>
</tr>
<tr>
<td>Disc area (mm²)</td>
<td>3.30 ± 0.99</td>
<td>2.02 ± 0.52</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Cup area (mm²)</td>
<td>0.10 ± 0.22</td>
<td>0.26 ± 0.33</td>
<td>0.012</td>
</tr>
<tr>
<td>NHV (mm³)</td>
<td>1.67 ± 0.67</td>
<td>0.56 ± 0.30</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Cup volume (mm³)</td>
<td>0.01 ± 0.05</td>
<td>0.04 ± 0.10</td>
<td>0.165</td>
</tr>
<tr>
<td>C/D area ratio</td>
<td>0.02 ± 0.07</td>
<td>0.12 ± 0.13</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>RNFL thickness (µm) average</td>
<td>166.35 ± 32.87</td>
<td>114.82 ± 10.96</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>RNFL thickness (µm) SH</td>
<td>168.76 ± 38.85</td>
<td>116.08 ± 14.03</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>RNFL thickness (µm) IH</td>
<td>163.01 ± 39.89</td>
<td>113.56 ± 10.39</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>GCC thickness (µm) average</td>
<td>95.52 ± 8.58</td>
<td>96.24 ± 6.39</td>
<td>0.627</td>
</tr>
<tr>
<td>GCC thickness (µm) SH</td>
<td>93.88 ± 8.07</td>
<td>96.32 ± 6.83</td>
<td>0.109</td>
</tr>
<tr>
<td>GCC thickness (µm) IH</td>
<td>97.16 ± 11.58</td>
<td>96.16 ± 6.41</td>
<td>0.568</td>
</tr>
</tbody>
</table>

NAION, nonarteritic anterior ischemic optic neuropathy; NRLT, neurosensorial retinal layer thickness; NHV, nerve head volume; SH, superior hemisphere; IH, inferior hemisphere; RNFL, retinal nerve fiber layer; GCC, ganglion cell complex.
The average RNFL thickness was significantly higher in the NAION group at 1 week post-onset and at 1 month after presentation compared, with the control group ($p < 0.05$), but then decreased to below control thickness over time (all $p < 0.05$) (Figure 3C). In new NAION patients, mean RNFL thicknesses of the superior and inferior retinal hemispheres were similar to the average RNFL thickness across the entire retina at all examination time points, while the mean RNFL thickness of the superior hemisphere was thinner than controls at 1 month ($p < 0.05$) (Figure 3C). The average GCC thickness in the NAION group was similar to that of the control group at 1 week, but then decreased significantly below the control mean over the next 3 months and remained below control GCC thickness for the remainder of the study period ($p < 0.001$) (Figure 3A).

Therefore, GCC (the sum of the RNFL, ganglion cell layer, and inner plexiform layer thicknesses) exhibited rapid contraction over the first 3 months after presentation (the acute phase), and this deficit was irreversible over the first year of the disease. Moreover, the reduction in thickness was relatively uniform across the retina. Visual acuity was significantly and positively correlated with the thickness of the superior hemisphere, inferior hemisphere, and total retinal average GCC thickness ($r = 0.344$, $r = 0.245$, $r = 0.304$, $p < 0.001$). The extent of the inferior VF deficit was also significantly correlated with both the superior hemisphere RNFL thickness and the superior hemisphere GCC thickness.

**Discussion**

NAION is typically characterized by degeneration of the prelaminar optic nerve due to short posterior ciliary artery insufficiency or occlusion with ensuing reduced blood supply to the optic papilla. However, a myriad of etiologies have been proposed for NAION and the pathophysiology has still not been fully explained, possibly because NAION is usually idiopathic and no risk factors have been identified and validated aside from older age. Nevertheless, some additional risk factors may exist (such as diabetes) since we observed NAION in early middle-aged patients. Nocturnal hypotension may cause axonal edema and optic disc congestion, leading to axonal degeneration and apoptosis of retinal ganglion cells (RGCs). This may explain the higher incidence of nocturnal onset NAION (blindness first noticed upon waking). Alternatively, insufficient drainage of this blood supply into the central retinal vein (i.e., venous insufficiency rather than arterial insufficiency) has also been suggested as a cause of NAION. Sleep apnea may also increase the risk for NAION. In general, any factor that can disrupt vascular autoregulation in these local vessels may cause NAION, as loss of blood supply or local edema may be particularly damaging in the optic nerve head due to the extremely high density of axons. Indeed, NAION is associated with retinal ganglion cell death, rather than just dysfunction, resulting in permanent loss of vision.

Quantitative analysis of peripapillary RNFL thickness by OCT can provide objective information for clinical application, and this technology has been used to examine

![Figure 3. Changes in GCC thickness. (A) Disc and cup morphus (B), and RNFL thickness and neurosensorial retinal layer thickness at the foveal region (C) over the 1 year course of NAION progression. All data are expressed as mean ± SD and significant differences in all parameters but cup volume were found among the groups ($p < 0.05$).](image-url)
morphological changes in the RNFL during glaucoma, Leber’s hereditary optic neuropathy, and traumatic optic neuropathy. More recently, OCT has been used for the quantitative study of optic disc lesions due to edema. Optic disc swelling is a common early feature of NAION, but it is not specific to NAION. In the current study, FD-OCT revealed both disc area and nerve head volume increases at 1 week after onset, while cup area and C/D area ratio were reduced compared with the control group, which is supported by a previous study. These morphometric changes indicate that crowding of the optic nerve head is severe in the early acute phase, possibly exacerbating ischemic damage. The neurosensory retinal layer thickness at the foveal region also was greater in NAION patients at one week, and there was significant peripapilledema. FD-OCT imaging revealed accumulation of subretinal fluid at this time in four of the 33 eyes, about the same fraction as reported previously (about 10%). Fluorescein angiograms showed no accumulation of dye in or around the macular region, indicating that the subretinal fluid was likely derived from the choroid circulation rather than from retinal blood vessels.

The RNFL thickness over the first month was thicker in NAION patients than in controls, consistent with peripapillary RNFL edema. These results do not completely agree with two previous studies, which may be due, at least in part, to the fact that the present study analyzed new-onset NAION (1 week), while a previous study assessed their patients within the first 6 months and the other made no mention of timing. However, the main difference and strength of the present study is that it benefited from a longitudinal assessment, while these two previous studies only studied a single time point. Only one other study used a longitudinal assessment of NAION using OCT in 16 diseased eyes and 14 control eyes (fellow unaffected eyes, while the present study included independent controls), and revealed different patterns of RNFL involvement according to the pattern of vision loss. Since the present study showed that eye parameters change in time after NAION onset, this could have led to a bias in these previous studies. Indeed, serial FD-OCT imaging indicated that both RNFL and GCC thickness gradually decreased over time without recovery. The GCC and superior hemisphere RNFL were thinner than in controls at one month post-onset, while the inferior hemisphere and average RNFL were not significantly reduced compared to controls until the 3-month scan. This suggests that degeneration of GCC may occur earlier than RNFL degeneration, possibly due to loss of dendrites. Contraction of RNFL and GCC layers occurred earlier in the superior hemisphere, thus explaining the higher frequency of inferior VF deficits observed in this patient group. Similarly, FD-OCT data established a similar correlation between lower hemisphere VF loss and superior RNFL thickness.

Deleon-Ortega et al. reported that RNFL as measured by Stratus OCT was more strongly correlated with Humphrey VF changes than was GDx-VCC. Both instruments revealed decreased RNFL thickness with altitudinal VF defects in NAION eyes, and both demonstrated RNFL loss even in sectors of the optic disc corresponding to relatively unaffected hemifields. Similarly, our analysis of the relationship between visual acuity and morphometric parameters using FD-OCT indicated that visual acuity was significantly and positively correlated with GCC thickness.

The visual impairments of NAION patients are likely related to the death of retinal ganglion cells. At 3 months after presentation and thereafter, neurosensory retinal layer thickness at the foveal region, total disc area, nerve head volume, cup area, and C/D area ratio were all similar to control values, while GCC thickness and RNFL thickness remained stable and below normal reference values, which is supported by previous studies. During the process of the disease, the rather faster decrease of thickness of RNFL and GCC in superior hemisphere may explain the greater defect of VF at inferior observed in the present study, which is also frequently in the clinic. Trip et al. observed significant correlations between VF loss and RNFL thickness in patients with optic neuritis after the first (and single) episode, suggesting that axonal loss was responsible for visual impairment.

We also observed partial PVD and traction at the surface of the optic disc during both early and advanced stages of NAION. We do not know, however, if this detachment resulted from optic disc swelling or if vitreal traction caused optic disc swelling. The role of vitreal traction in the pathogenesis of NAION remains to be studied.

The present study suffers from some limitations. Indeed, the sample size was small, which could have prevented to observe much improvement in visual acuity after NAION onset, which was suggested by a previous study, and preventing us to make subgroup analyses. In addition, the follow-up was relatively short, and it might be interesting to assess a longer follow-up. Finally, treatment timing was not explored. Indeed, a previous in vivo study revealed that the therapeutic window for NAION might be as long as 2–3 weeks, while we performed FD-OCT at 1 week, and 1, 3, 6, and 12 months after onset, which is the standard of care at our institution. Prospective observational studies with a larger number of FD-OCT assessments might provide more information about evolution of NAION in time and the best therapeutic timing approach.

In conclusion, NAION progression is characterized by an initial phase of accelerated RNFL and GCC deterioration. These results reveal the kinetic change of neural retina in NAION and may have implication on the time window for treatment of NAION. FD-OCT is useful in the evaluation of NAION.

Declaration of interest

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

References


