• Clinical Research •

Acute changes in ganglion cell layer thickness in ischemic optic neuropathy compared to optic neuritis using optical coherence tomography

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Abstract

● **AIM:** To elucidate the changes of different ganglion cell layer (GCL) thinning patterns between the optic neuritis (ON) and non-arteritic anterior ischemic optic neuropathy (NAION).

● **METHODS:** A prospective, observational study was conducted to evaluate the timing of GCL changes between acute ON and NAION using optical coherence tomography.

● **RESULTS:** Thinning on optical coherence tomography in the NAION group occurs as early as 11d after symptomatic onset of vision loss and follows an altitudinal pattern. The mean superior-inferior GCL thickness difference in the NAION cohort was clinically significant at 5.7 μm in the NAION cohort compared to controls of 0.8 μm (*P*=0.032), but not significant in the ON group compared to controls with both groups measuring 1.1 μm. Global thinning was significant for the ON group compared to controls at 7.2 μm (*P*=0.011) but not the NAION group compared to controls at 1.35 μm.

● **CONCLUSION:** These findings suggest that future treatments for NAION should be given early, and possibly before 11d in order to prevent GCL and irreversible vision loss.

● **KEYWORDS:** optic neuritis; non-arteritic ischemic optic neuropathy; optical coherence tomography; ganglion cell layer

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INTRODUCTION

In adults, the two most common optic neuropathies are optic neuritis (ON) and non-arteritic anterior ischemic optic neuropathy (NAION). ON responds well to steroids, but often patients are still left with subtle visual dysfunction. One study in India has placed the incidence of NAION at 37.8% and ON at 28.9% of patients presenting with acute disk edema[1]. There is no proven treatment for NAION, though clinical trials are currently underway. Still, the exact treatment and timing of treatment remain unknown. A better understanding of the changes to the optic nerve and ganglion cell layer (GCL) may help better direct therapies in the future.

ON and NAION also share some overlapping clinical features, which poses some difficulty in distinguishing between the two. However, the diagnosis may generally be made based on age, pain with eye movements, pattern of visual field loss and visual recovery. More recently, different thinning patterns between these two entities have been demonstrated on optical coherence tomography (OCT) by others[2]. Optic disc edema is most commonly associated with NAION, although it may also be seen with one-third of ON cases[3-4]. In this study, we will further evaluate the timing of GCL changes between acute ON and NAION using OCT.

SUBJECTS AND METHODS

Ethical Approval The Aravind Eye Care System Institutional Review Board approved the study. The study was conducted in accordance with the principles of the Declaration of Helsinki. Informed consent was obtained from all patients.

A prospective, observational, single centre study of consecutive patients was performed in the Outpatient Department of Aravind Eye Hospital, Coimbatore, India between January to May 2017 to compare the mean GCL thickness between eyes in two groups: ON and NAION. Healthy, age-matched controls, evaluated with OCT were used for a case control analysis.

Forty patients with acute ON and their age-matched controls as well as 40 patients with acute NAION and their age-matched controls were enrolled. Dilated fundus exam was done to assess for disk edema followed by HD-OCT (Heidelberg Spectralis, Heidelberg Engineering, Heidelberg, Germany) to assess the mean GCL thickness. Special attention was paid

Table 1 Mean GCL thickness in superior and inferior quadrants and global GCL thickness in ON, NAION and controls μm

Parameters	ON	ON-control	NAION	NAION-control
Mean superior GCL thickness	63.4	71.7	66.9	71.5
Mean inferior GCL thickness	64.5	70.6	72.6	70.7
Superior-inferior GCL thickness difference	1.1	1.1	5.7	0.8
Mean global GCL thickness	63.95	71.15	69.75	71.1
Global GCL thickness difference	7.2		1.35	

GCL: Ganglion cell layer; ON: Optic neuritis; NAION: non-arteritic anterior ischemic optic neuropathy.

to the superior and inferior quadrants and the differences in absolute values in ON and NAION were compared between.

Patients had to meet all the following criteria to be included in the NAION group: disc edema; no eye pain or headache; sudden visual loss; Humphrey visual field with altitudinal field defect; colour deficit; haemorrhages of the optic nerve head; crowding of the optic disc in the other eye; normal erythrocyte sedimentation rate [<(age+10)/2 for women and <age/2 for men] and C-reactive protein (<3 mg/L); age>18y; interval<3wk from onset of symptoms; no prior treatment.

Patients had to meet all the following criteria to be included in the ON group: no previous ON; interval<3wk from onset of symptoms; pain with eye movements; Humphrey visual field with a central scotoma; colour deficit checked using Ishihara plates; mild or no optic disc swelling; improvement on subsequent examination; magnetic resonance imaging of the orbits with optic nerve enhancement; age>18y; interval<3wk from onset of symptoms; no prior treatment.

Based on the diagnostic criteria, patients were selected after a complete neuro-ophthalmological examination which included the assessment of the best corrected visual acuity, using a standard Snellen chart. Colour vision discrimination was assessed using Ishihara charts. Fundus examination was done using Heidelberg Spectralis high definition OCT (HD-OCT). Using standard acquisition protocol, each subject's eyes were scanned on the day of presentation to our institution. The macular cube line scans were used to assess GCL.

The scanned area was 6 mm, in the protocol, with no signal averaging. Signal strength (0-10 arbitrary units) was used to assess the quality of the obtained images. Signal strength of 6 units or more was needed for inclusion in the study. Automatic algorithms were used to determine GCL thickness, using HD-OCT.

GCL analysis was done by calculating the thickness of the GCL and the inner plexiform layer. The GCL thickness was measured around the fovea in seven locations: supero-temporal, superior, superior-nasal, infero-nasal, inferior, infero-temporal and global. The average, minimum and sectorial thickness of the GCL were measured in an elliptical annulus around the fovea. Global GCL thickness values, and those in each of the said locations, expressed in micrometers (μm), were used for analysis.

MRI was performed on either a Siemens Skyra 3T or Philips ingenia 1.5T. Sequences obtained for the optic nerve evaluation incuded T2 fat saturated axial, IR coronal, DWI, post contrast fat saturated T1 in all planes.

RESULTS

Each cohort (NAION and ON) included 40 eyes. In the NAION cohort, the mean age was 61.3±10.6y while in the ON cohort it was 35.9±11.6y. For the age-matched control cohorts, the mean age was 62.0±11.8y and 35.0±11.6y, respectively. Of the 40 subjects in the NAION cohort, 13 were women while 21 were women in the ON cohort. For the age-matched controls in the ON cohort, 14 were women while 23 were in the NAION age-matched control group. Mean time from the start of symptoms to presentation was 10.7±6.6d in the NAION cohort while it was 11.7±8.6d in ON (P=0.67) with a range of 3-22d.

There was a significant superior-inferior difference in GCL thickness in the NAION cohort but not in the ON cohort. The mean superior-inferior GCL thickness difference in the NAION cohort was clinically significant at 5.7 μm in the NAION cohort compared to controls of 0.8 μm (P=0.032), but not significant in the ON group compared to controls with both groups measuring 1.1 μm (Table 1). However, global thinning was significant for the ON group compared to controls at 7.2 μm (P=0.011) but not the NAION group compared to controls at 1.35 μm (P=0.685; Table 1).

DISCUSSION

In this study we have shown that ganglion cell loss occurs an altitudinal pattern in NAION, resulting in an asymmetric thinning of the superior and inferior GCL hemispheres of the macula. This asymmetric thinning is not seen in ON or in healthy controls. This asymmetric change had a mean of 5.7 μm in NAION subjects. Moreover, this change is evident as early as a mean of 11d after onset of symptoms. In ON, the GCL thinning is global, but also present at a mean of 11d. The global thinning in NAION, on the other hand, does not reach significance, since the hemispheric thinning is countered by the lack of thinning in the contralateral hemisphere in the GCL.

The most common visual field defect in NAION is an altitudinal one, whereas in ON, the visual field loss is more likely to a central scotoma or diffuse[5-7] and both of these clinical findings correspond with the GCL thinning patterns we have demonstrated in each respective group. The segmental ischaemia of the optic nerve in NAION commonly presents with disc edema, and may be followed by damage to other areas of the optic nerve[8-9]. Aggarwal *et al*[2] demonstrated in NAION that at six months after presentation, if the visual field loss was superior or inferior, it correlated with GCL thinning. However, there was both superior and inferior GCL hemisphere thinning in 16 out of 23 eyes in their study.

In this study, we demonstrated that thinning of the GCL may be seen in NAION and ON as early as a mean of 11d after symptoms begin when compared to age-matched controls, which is consistent with a retrospective study by Erlich-Malona *et al*[10] and a prospective study by De Dompablo *et al*[11]. However, to the best of our knowledge, this early change in GCL thickness has not been reported before in a prospective study of both NAION and ON.

Previous studies have also shown similar asymmetric retinal nerve fibre layer (RNFL) thinning in NAION, but demonstrated this thinning at 6mo after symptom onset, when the optic nerve edema had resolved[7-12]. Others have suggested that GCL thickness may be a better measure of damage in both ON[13-16] and NAION[2,17] during the acute phase, since the GCL is not affected by the initial edema the way the retinal nerve fibre layer frequently is in ON and universally is in NAION. Our findings suggest that GCL loss can be seen at a mean of less than 2wk.

Kupersmith *et al*[16] studied patients with multiple sclerosis (MS) and found a significant difference in GCL thickness between affected and unaffected eyes at 1mo after onset of ON. However, there was no significant difference in GCL thickness at presentation[16]. The initial difference may have been underestimated due to progressive, subclinical GCL thinning that has been seen in clinically normal eyes of patients with MS[14,18]. Our prospective study, however, did find GCL thinning as early as 11d after symptom onset in both NAION and ON. Our study compared subject eyes with control eyes from normal patients, thus removing the effect of subclinical contralateral GCL thinning in MS patients.

Some authors have shown that disc edema in NAION patients may resolve faster when systemic corticosteroids are administered within 2wk of onset, and that they may also enjoy better visual acuity and field recovery[14]. Experimental models have suggested that the initial disc swelling in NAION results in a type of compartment syndrome from the surrounding nerve sheath that leads to ischaemic damage[19-21]. This theory supports the early treatment of this initial swelling to reduce the deleterious effect of the compartment syndrome on the neurons and visual loss.

Our study has demonstrated that there is an asymmetric thinning of the GCL, as measured with OCT, and that this asymmetry is significantly greater in NAION than in ON. This finding may be used to help differentiate the two. More importantly, our findings help in the recognition of acute GCL loss in both NAION and ON which may help guide appropriate and early treatment to prevent permanent vision loss. Currently there is no known treatment for NAION and the treatment protocol for ON in the ON treatment trial required intervention within 8d of symptom onset. However, our results suggest that by as early as a mean of 11d, GCL thinning has occurred, and possibly future treatments should aim at intervention within days or even hours of symptom onset to prevent early GCL loss.

Our study has a few limitations including not differentiating the various causes of ON, small sample size, lack of contrast in all patient MRI studies and lack of randomization. Future studies on this topic should include a prospective, randomized study with serial OCTs to help in detailed evaluation of the GCL thickness in both NAION and ON, particularly in the early days after symptom onset.

In conclusion, though clinical assessment remains the mainstay of diagnosing ON and NAION, OCT-GCL thinning patterns might aid in differentiating the two when the diagnosis is not certain. Moreover, the thinning that occurs in both NAION and ON appears to occur as early as 11d after symptom onset. Our findings suggest that the changes to the GCL occur early, and successful treatments to prevent GCL and vision loss may need to be applied within days or even hours after symptom onset.

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