Optic Disc Evaluation by Optical Coherence Tomography in Nonarteritic Anterior Ischemic Optic Neuropathy

Inés Contreras,1 Gema Rebolleda,1,2 Susana Noval,1 and Francisco J. Muñoz-Negrete1,2

PURPOSE. To describe the characteristics of the optic nerve head (ONH) in patients with nonarteritic anterior ischemic optic neuropathy (NAION) and compare them with control subjects by using optical coherence tomography (OCT).

METHODS. Patients with NAION underwent a complete ophthalmic examination, including OCT scanning of the ONH at diagnosis. The examination was repeated 1.5, 3, and 6 months later. Age- and sex-matched control subjects with no ocular disease underwent a similar evaluation. Data were obtained by using the ONH analysis protocol of the StratusOCT (Carl Zeiss Meditec, Dublin, CA).

RESULTS. Twenty-three patients and 23 control subjects were included. In eyes with NAION, the vertical integrated rim area decreased significantly ($P < 0.01$) from the acute phase to the 6-month visit. The cup-to-disc (C/D) area ratio increased significantly ($P = 0.002$) from the acute examination to the 3-month visit. There was a significant difference between the NAION fellow eyes and the control eyes in C/D ratio, evaluated by slit lamp funduscopy ($P < 0.001$), and in the C/D area ratio ($P = 0.001$). The vertical integrated rim area was significantly ($P = 0.001$) greater in NAION fellow eyes than in control eyes. There was no significant difference in optic disc area or vertical disc diameter among the control eyes, NAION-affected eyes, and NAION fellow eyes.

CONCLUSIONS. Although patients with NAION have lower C/D ratios than does the normal population, with a higher level of nerve fiber crowding, there was no difference in optic disc size between patients with NAION and control subjects. After the development of NAION, 47.8% of eyes had a C/D ratio that differed from that in the fellow eye by more than 0.1. (Invest Ophthalmol Vis Sci. 2007;48:4087–4092) DOI:10.1167/iovs.07-0171

Nonarteritic anterior ischemic optic neuropathy (NAION) is believed to result from transient hypoperfusion or nonperfusion in a so-called disc at risk.1,2 These discs have been described as having a small or nonexistent physiologic cup, with crowding of the retinal nerve fibers.3–6 Studies performed with the Heidelberg Retina Tomograph (HRT; Heidelberg Engineering, Heidelberg, Germany) have confirmed the presence of a smaller physiologic cup in patients with NAION but reported no difference in the size of the optic nerve head (ONH).7,8 However, no studies have analyzed the characteristics of the ONH in patients with NAION with optical coherence tomography (OCT), an imaging method that has been used extensively to measure the retinal nerve fiber layer (RNFL) thickness and to study the ONH in patients with glaucoma.9–14 Although its applications in neuro-ophthalmology have been more limited, OCT also may be a useful tool in this field.15–20

The purpose of this study was to describe the characteristics of the ONH in patients with NAION and to use OCT to compare them with those in subjects with no known ocular diseases.

METHODS

All patients with NAION diagnosed in our center between April 1, 2004, and March 31, 2006, were considered for inclusion. These patients had been evaluated prospectively as part of a larger observational study. They were evaluated within 3 days of diagnosis by one of the authors (IC, SN, or GR). Diagnosis of NAION was based on sudden loss of visual acuity (VA); disc edema on fundus ophthalmoscopy; visual field defects consistent with NAION; erythrocyte sedimentation rate and reactive protein C levels within normal values, with no signs or symptoms suggestive of giant cell arteritis; and resolution of disc edema in 2 months. Exclusion criteria were visual loss of more than 2 weeks’ duration, the presence of an ocular disease other than NAION, and the presence of systemic diseases that precluded adequate follow-up and examination. Cataract surgery in the affected eye was not an exclusion criterion. All participants provided informed consent to be included in the study according to the Declaration of Helsinki. The study was approved by the ethics committee.

Patients underwent a complete ophthalmic examination, including Snellen VA, Goldmann applanation tonometry, slit lamp evaluation of the anterior and posterior poles (including estimation of the vertical cup-to-disc [C/D] ratio), standard automated perimetry with the SITA (Swedish Interactive Threshold Algorithm) 24-2 strategy, and OCT scanning of the ONH. This examination was repeated at 6 weeks and 3 and 6 months after the acute episode.

Age- and sex-matched control subjects were recruited from among the workers at our center and the relatives of patients. They underwent the same tests as the patients. Exclusion criteria were Snellen VA worse than 20/40 or the detection of an ocular disease.

OCT scanning was performed with StratusOCT (Carl Zeiss Meditec, Dublin, CA) by two of the authors (IC, SN) after pharmacologic mydriasis. Image acquisition was performed with the Fast RNFL (3.4) and the Fast Optic Disc protocols. Good-quality scans (signal score of 4 or higher) were saved as soon as they appeared. The RNFL thickness was obtained with the StratusOCT RNFL Thickness Average analysis protocol and the ONH parameters with the Optic Nerve Head Analysis protocol. Before recording these values, one author (IC) checked that the OCT software had correctly identified the limits of the optic nerve and manually reset them when necessary (Fig. 1). The ONH analysis protocol searches for the limits of the retinal pigment epithelium (RPE)/choriocapillaris layer and sets the disc margins at its ends. A straight line connects the edges of the

From 1Ramón y Cajal Hospital, Madrid, Spain; and 2Alcalá University, Alcalá de Henares, Spain.

Submitted for publication February 10, 2007; revised March 28 and May 6, 2007; accepted June 8, 2007.

Disclosure: I. Contreras, None; G. Rebolleda, None; S. Noval, None; F.J. Muñoz-Negrete, None

The publication costs of this article were defrayed in part by page charge payment. This article must therefore be marked ‘advertisement’ in accordance with 18 U.S.C. §1734 solely to indicate this fact.

Corresponding author: Inés Contreras, c/Martín de los Heros nº80 5°D, 28008, Madrid, Spain; ineson3@yahoo.com.


Copyright © Association for Research in Vision and Ophthalmology

4087
RPE/choriocapillaris layer, and a second line is drawn 150 μm anterior and parallel to the first one (Fig. 1). Structures below this last line are defined as the disc cup and above this line as the neuroretinal rim. For the C/D ratio, the OCT software assigns a value of 1.0 in the absence of a physiologic cup (Fig. 1); in these cases, the C/D ratio was recorded as 0.0. The values recorded were the vertical disc diameter, the vertical integrated rim area (VIRA), the disc area, the C/D area ratio, the C/D horizontal ratio, and the C/D vertical ratio. The VIRA is an estimate of the total volume of RNFL tissue in the rim, calculated by multiplying the average individual rim area times the circumference of the disc.

Statistical analysis was performed with commercial software (SPSS, ver. 12.0; SPSS, Chicago, IL). Given the small sample size, we used nonparametric tests. Since multiple comparisons were performed according to the Bonferroni correction method, the final level of significance was set to 0.002 (two-sided).

RESULTS

Twenty-seven patients (14 men, 13 women) with NAION were evaluated. Mean age was 66.7 years (SD, 9.7). Mean time from onset to initial examination was 5.0 days (SD, 4.7). Three patients had had an episode of NAION in the fellow eye and were excluded from statistical analysis, as was one patient with pathologic myopia. Three patients had undergone cataract surgery between 5 and 14 days before the onset of NAION. Approximately 40% of the ONH scans had to have the limits of the RPE manually redefined.

Twenty-three age- and sex-matched control subjects were recruited. A comparison between ONH parameters and overall RNFL thickness between the right and left eyes of this control group did not show any significant difference (data not shown). In patients with NAION, the values of the ONH pa-
TABLE 1. ONH Parameters for the Affected and Fellow Eye over Time

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Control</th>
<th>NAION Fellow Eye</th>
<th>NAION Affected Eye</th>
</tr>
</thead>
<tbody>
<tr>
<td>C/D Area Ratio</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Acute (n = 23)</td>
<td>0.05 (0.10)</td>
<td>0.13 (0.15)</td>
<td>—</td>
</tr>
<tr>
<td>3 Months (n = 23)</td>
<td>0.21 (0.19)</td>
<td>0.14 (0.13)</td>
<td>—</td>
</tr>
<tr>
<td>6 Months (n = 20)</td>
<td>0.24 (0.19)</td>
<td>0.15 (0.16)</td>
<td>—</td>
</tr>
<tr>
<td>Vertical Integrated Rim Area (mm³)</td>
<td>4.14 (2.09)</td>
<td>0.91 (0.52)</td>
<td>4.45 (1.25)</td>
</tr>
<tr>
<td>Disc Area (mm²)</td>
<td>4.56 (0.44)</td>
<td>2.56 (0.44)</td>
<td>2.48 (0.52)</td>
</tr>
<tr>
<td>Vertical C/D Ratio</td>
<td>0.47 (0.14)</td>
<td>0.91 (0.55)</td>
<td>0.93 (0.54)</td>
</tr>
<tr>
<td>Disc area (mm²)</td>
<td>0.961</td>
<td>2.64 (0.55)</td>
<td>1.94 (0.27)</td>
</tr>
<tr>
<td>C/D horizontal ratio</td>
<td>0.307</td>
<td>0.91 (0.55)</td>
<td>2.64 (0.55)</td>
</tr>
<tr>
<td>Disc area (mm²)</td>
<td>0.961</td>
<td>2.64 (0.55)</td>
<td>1.94 (0.27)</td>
</tr>
<tr>
<td>C/D vertical ratio</td>
<td>0.63 (0.47)</td>
<td>0.91 (0.55)</td>
<td>2.60 (0.47)</td>
</tr>
<tr>
<td>Disc area (mm²)</td>
<td>0.961</td>
<td>2.64 (0.55)</td>
<td>1.94 (0.27)</td>
</tr>
<tr>
<td>C/D area ratio</td>
<td>0.47 (0.14)</td>
<td>0.91 (0.55)</td>
<td>0.93 (0.54)</td>
</tr>
<tr>
<td>Disc area (mm²)</td>
<td>0.961</td>
<td>2.64 (0.55)</td>
<td>1.94 (0.27)</td>
</tr>
<tr>
<td>Vertical disc diameter (mm)</td>
<td>1.96 (0.33)</td>
<td>2.03 (0.39)</td>
<td>2.03 (0.39)</td>
</tr>
<tr>
<td>Mean RNFL (µm)</td>
<td>92.40 (18.78)</td>
<td>94.62 (21.28)</td>
<td>56.94 (11.94)</td>
</tr>
</tbody>
</table>

Data are expressed as the mean (SD). Comparisons were performed with the Mann-Whitney test. n, number of patients.

On slit lamp funduscopy, 81.5% of the fellow eyes of patients with NAION had a vertical C/D ratio of 0.1 or less, with 40.7% of these having no physiologic cup. The mean vertical C/D ratio on funduscopy was 0.1 (SD, 0.13). In the control group, the mean vertical C/D ratio was 0.29 (SD, 0.1) and 95.6% of patients had a difference in the C/D ratio between the right and left eyes that was equal to or lower than 0.1. There were no significant differences in the parameters included in the analysis. Data from the 3-month visit of patients with NAION and the control group, one eye was randomly selected from each subject in the control group to be included in the analysis. From the 3-month visit of patients with NAION of the affected and fellow eyes were compared with the eyes in the control group. There was a significant difference between the NAION fellow eye and the control eye in the C/D vertical ratio, as evaluated by slit lamp funduscopy, and in the C/D area ratio and C/D vertical ratio, with lower values for all these parameters in the NAION fellow eye (Table 2). There were no significant differences in the parameters between control eyes and NAION-affected eyes or between NAION-affected and fellow eyes.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Control</th>
<th>NAION Fellow Eye</th>
<th>NAION Affected Eye</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vertical C/D ratio on funduscopy</td>
<td>0.29 (0.13)</td>
<td>0.10 (0.13)</td>
<td>—</td>
</tr>
<tr>
<td>C/D area ratio</td>
<td>0.27 (0.14)</td>
<td>0.14 (0.13)</td>
<td>0.21 (0.19)</td>
</tr>
<tr>
<td>C/D horizontal ratio</td>
<td>0.52 (0.17)</td>
<td>0.36 (0.22)</td>
<td>0.41 (0.27)</td>
</tr>
<tr>
<td>C/D vertical ratio</td>
<td>0.47 (0.14)</td>
<td>0.30 (0.18)</td>
<td>0.38 (0.25)</td>
</tr>
<tr>
<td>Vertical integrated rim area (mm³)</td>
<td>0.47 (0.23)</td>
<td>0.93 (0.54)</td>
<td>0.75 (0.49)</td>
</tr>
<tr>
<td>Disc area (mm²)</td>
<td>2.49 (0.43)</td>
<td>2.64 (0.55)</td>
<td>2.64 (0.52)</td>
</tr>
<tr>
<td>Vertical disc diameter (mm)</td>
<td>1.96 (0.33)</td>
<td>2.03 (0.39)</td>
<td>1.94 (0.26)</td>
</tr>
<tr>
<td>Mean RNFL (µm)</td>
<td>92.40 (18.78)</td>
<td>94.62 (21.28)</td>
<td>56.94 (11.94)</td>
</tr>
</tbody>
</table>

Data are expressed as the mean (SD). Comparisons were performed with the Mann-Whitney test.

DISCUSSION

Jonas et al.²¹ performed an extensive evaluation of ONH topography in normal eyes through magnification-corrected morphometry of optic disc photographs. Side differences in the optic disc area of 0.50 mm² or less were found in 84% of subjects; mean vertical and horizontal C/D ratios were 0.34 and 0.39, respectively. Others have reported similar estimates for normal C/D ratios.²²,²³ Further studies have reported that the difference in the C/D ratio between the right and left eyes of an individual is less than 0.1 in up to 98% of cases.²⁴,²⁵ Thus, investigators who evaluated whether a small physiologic cup is involved in the pathogenesis of NAION usually analyzed the C/D ratio of the unaffected fellow eye, since it is taken for

At the 3-month visit, 47.8% of eyes with NAION had a C/D area ratio that differed from the fellow eye by more than 0.1. The mean C/D area ratio was 50% higher in the affected eye than in the fellow eye. The VIRA was significantly higher in NAION fellow eyes than in control eyes (Mann-Whitney test, \( P = 0.001 \)).

There was no significant difference in the optic disc area and vertical disc diameter between the three groups at the 3-month visit. Mean RNFL thickness decreased in the NAION-affected eye compared with fellow and control eyes (Mann-Whitney test, \( P < 0.001 \) for both comparisons; Table 2). In the NAION fellow eyes, mean RNFL thickness did not correlate with disc area or vertical disc diameter (\( r = 0.11 \) and \( r = 0.31 \), respectively). Nor did mean RNFL thickness correlate with disc area (\( r = 0.190 \), \( P = 0.168 \)), or vertical disc diameter (\( r = 0.102 \), \( P = 0.461 \)) in control eyes.

Jonas et al.²¹ performed an extensive evaluation of ONH topography in normal eyes through magnification-corrected morphometry of optic disc photographs. Side differences in the optic disc area of 0.50 mm² or less were found in 84% of subjects; mean vertical and horizontal C/D ratios were 0.34 and 0.39, respectively. Others have reported similar estimates for normal C/D ratios.²²,²³ Further studies have reported that the difference in the C/D ratio between the right and left eyes of an individual is less than 0.1 in up to 98% of cases.²⁴,²⁵ Thus, investigators who evaluated whether a small physiologic cup is involved in the pathogenesis of NAION usually analyzed the C/D ratio of the unaffected fellow eye, since it is taken for
granted that before the episode of NAION both eyes had similar ONHs. Studies performed by measuring stereoscopic photographs or slit lamp evaluation have reported that patients with NAION have lower C/D ratios than those in the normal population, with a higher incidence of an absent physiologic cup.\textsuperscript{3-6} In accordance with these publications, we found that 40.7% of fellow eyes of patients with NAION had no physiologic cup. The estimated mean vertical C/D ratio in fellow eyes on slit lamp funduscopy was 0.1 (SD, 0.1). In the control group, the mean vertical C/D ratio was 0.29 (SD, 0.1). Regarding optic disc area, Jonas et al.\textsuperscript{9} reported an area of 2.57 ± 0.29 mm\textsuperscript{2} in NAION fellow eyes compared with 2.69 ± 0.7 mm\textsuperscript{2} in control eyes. Mansour et al.\textsuperscript{26} also found that the ONH of fellow eyes of patients with NAION was slightly smaller than in control subjects.

To date, few studies have been performed to measure the C/D ratio in NAION with objective methods, since both slit lamp examination and photographic planimetry are affected by the examiner’s experience and perception. Saito et al.\textsuperscript{27} who compared the ONH parameters obtained with the HRT between the fellow eyes of patients with NAION and patients with open-angle glaucoma (OAG), found that the C/D ratio was significantly smaller in patients with NAION, whereas the rim area was larger than that in patients with OAG. No difference was found in disc area between both groups. Danesh-Meyer et al.\textsuperscript{34} evaluated the ONH in patients after NAION and arteritic anterior ischemic optic neuropathy (AAION) with the HRT. The C/D area was 42% larger in the affected eyes in the NAION group than in the fellow eyes. There was no difference in disc area between both groups. However, a disadvantage of the studies performed with HRT is that the disc margin was drawn by a trained observer, introducing subjectivity into image analysis.

OCT is a new imaging technique that can obtain retinal images with a resolution of up to 10 μm.\textsuperscript{9,10,14} The repeatability of the ONH measurements with the StratusOCT is moderately good,\textsuperscript{27,28} although OCT tends to provide higher C/D ratios than those estimated by slit lamp evaluation.\textsuperscript{27} The present study was undertaken to determine the characteristics of the ONH of patients with NAION, as measured by OCT.

In accordance with previous studies, slight or no differences were found in ONH parameters between the right and left eyes of control subjects, confirming the validity of evaluating changes in the ONH in NAION by comparing the affected with the fellow eye. The C/D area ratio was 0.27, the disc area 2.49 mm\textsuperscript{2}, and the vertical disc diameter 1.96 mm in the control group. These values were similar to those obtained through magnification-corrected morphometry of optic disc photographs,\textsuperscript{21} although higher than those obtained in HRT studies.\textsuperscript{3-6} This difference could be because ONH measurements obtained with HRT tend to be consistently lower than OCT measurements.

In NAION, disc edema results in a large disc area and vertical disc diameter because the presence of subretinal fluid masks the RPE near the ONH, leading to measurement artifacts caused by the failure of the scan to detect the RPE. When disc edema resolves, the RPE reappears in the scan so that the ONH measurements can be performed accurately, and the disc area and vertical disc diameter decrease (Table 1). Comparisons among the control, NAION-affected, and fellow eyes were performed at the 3-month visit, when disc edema has resolved, to allow inclusion of the highest number of patients possible. The C/D area ratio and the vertical C/D ratio measured by OCT were significantly higher in control patients than in NAION fellow eyes. This finding agrees with previous studies and supports the hypothesis that a crowded nerve head is involved in the pathogenesis of NAION. Transient hypo- or nonperfusion leads to nerve fiber edema: In a crowded nerve, this edema compromises the microvasculature of the ONH, leading to more ischemia and finally to NAION. In an ONH with physiological cupping, in which initial edema does not compromise blood flow, spontaneous resolution may occur. The VIRA was significantly higher in NAION fellow eyes compared with the control group, even in the presence of similar disc areas and vertical disc diameters, which suggests more crowding in eyes in which NAION develops. We did not find a difference in disc area and disc diameter between control subjects and NAION-affected or fellow eyes. Even if this can be attributed to the small sample size, other studies performed with HRT also did not report a difference.\textsuperscript{7,8}

There is controversy about the existence of a relationship between the nerve fiber count and optic nerve size.\textsuperscript{3,4} Savini et al.\textsuperscript{3,4} found in normal white subjects that the RNFL thickness increased significantly with an increase in optic disc size. However, other investigators did not find any significant correlation.\textsuperscript{5,35,36} It is unclear whether eyes with large ONHs have a thicker RNFL because of more nerve fibers or because of a shorter distance between the circular scan and the optic disc edge, since the RNFL thickness decreases at increasing distances from the ONH.\textsuperscript{21,23,25,26} In the present study, we did not find a significant correlation between mean RNFL thickness and disc size. Histopathologic studies have proven that there is a wide range of “normal” retinal nerve fiber counts in the optic nerve\textsuperscript{15,37,38}; therefore, there may be a tendency toward the presence of a larger number of fibers in larger optic discs that is masked by the wide range of normal values.

Despite the RNFL loss that occurs after NAION, cupping is rarely detected, as opposed to eyes with AAION.\textsuperscript{34,39} Rather, the discs are described as pale. The explanation usually provided for this phenomenon is that in AAION the ischemic insult is more intense, whereas in NAION there is just transient hypoperfusion, leading to less tissue damage. Another more plausible hypothesis is that cupping in eyes with NAION is more difficult to detect because of the previously small or absent physiologic cup and the development of optic disc pallor. Our finding that the C/D area ratio increases 50% after NAION compared with the fellow eye, together with the similar value found by Danesh-Meyer et al.,\textsuperscript{19} favors the second hypothesis.

The main limitation of this study was the relatively small number of patients. However, to the best of our knowledge, ours is the first prospective, controlled study to compare ONH parameters in NAION by using a quantitative and objective test. Another problem is that ONH measurements performed with OCT are not completely objective, inasmuch as it is necessary to correct manually the limits of the RPE identified by the OCT software. Approximately 40% of scans required that the RPE limits be redefined. Even if this introduces a subjective bias, an idea of the validity and repeatability of this technique can be obtained from the low variation in ONH parameters of the fellow eye measured at different time points in patients with NAION.

In conclusion, we have confirmed that patients with NAION have lower C/D ratios than the normal population, with a higher level of nerve fiber crowding (high VIRA). However, we did not find a difference in optic disc size between patients with NAION and control patients as previously reported.\textsuperscript{5,26} Nor was there a correlation between the overall mean RNFL thickness and optic disc size. The paradoxical finding of a higher VIRA in NAION fellow eyes compared with control eyes in the presence of a similar optic disc size and similar RNFL thicknesses may be related to more anterior position of the lamina cribrosa in patients with NAION. The methodology of OCT also must be considered. In optic nerves in which the...
optic cup is deeper, the nerve fibers have more space as they enter the optic discs, and some of them could even escape counting by the OCT software. In optic discs with a shallower cup, an identical number of fibers are more densely packed, and all fibers would probably be included in the OCT measurement.

References


