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Ganglion Cell Layer Analysis in Nonarteritic Anterior Ischemic Optic Neuropathy in Diabetic Patients: From the Acute to Resolving Phases

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ABSTRACT

Purpose: The aim of the present study was to assess tomographic changes in CGC in diabetic patients with non-arteritic anterior ischemic optic neuropathy (NOIA-NA) over a 6-month period and to investigate possible correlations with visual acuity and DM.

Materials and methods: This is a prospective observational study, conducted at a diabetes referral centre between January 2017 and January 2020. All patients received a complete ophthalmological examination including measurement of best corrected visual acuity (BCVA), a standard automated visual field, and optical coherence tomography of the papilla (the peripapillary retinal nerve fibre layer RNFLp) and macula (the ganglion cell layer). Patients were monitored at 3 and 6 months. At each follow-up visit, visual acuity measurement, OCT, and CV were performed. CGC measurements in the affected eyes were compared with those of a control group. Correlations between the thinning of the CGC and functional parameters such as MAVC and mean deviation (MD) in the acute and chronic phases were analyzed.

Results: We included 80 eyes of 80 diabetic patients with NOIA-NA corresponding to our inclusion criteria. The average age was 60.78 ± 6.88 years with extremes ranging from 40 to 75 years, sex ratio F/H=1.28. The mean CGC thickness was 76.93 ± 2.96 µm and 80.03 ± 1.03 µm in affected and control eyes, respectively (P=0.001). Compared to the normative OCT baseline, 62.5% of affected eyes showed thinning of the CGC thickness. In contrast, 100% of the eyes showed RNFLp thickening. The rate of CGC thinning increased over time, such that by the third month, 100% of the eyes with NOIA-NA in our study were classified as abnormal. The CGC was significantly thinner between the initial visit and 3 months (76.93 ± 2.96 µm vs. 67.12 ± -3.33 µm P<0.001) and significantly thinner between the third month follow-up and 6 months (67.12 ± -3.33 µm vs. 66.56+/-3.4 µm P<0.03). The mean percentage of CGC loss after the acute episode was 12.75% (9.81 µm) at 3 months and 13.47% (10.37 µm) at 6 months. CGC at the initial visit was found to be significantly associated with VA (r=-0.682; p<0.001) and DM (r=0.946; p<0.001). Similarly, mean CGC thickness at 3 months and 6 months follow-up was significantly associated with VA (r=-0.633, p<0.001 at 3 months and r=-0.654, p<0.001 at 6 months) and DM (r=0.877, p<0.001 at 3 months and r=0.811; p<0.001 at 6 months).

Conclusion: This study indicates that early lesions of the CGC occur in diabetic patients with NOIA-NA in the acute phase, that these lesions can be accurately measured with OCT, and that the significant correlation between CGC changes and visual field deficits and VA represents an important structure-function relationship and underscores the importance of OCT in the evaluation of the functional and structural course of eyes with NOIA-NA.

Key words: Nonarteritic anterior ischemic optic neuropathy, Diabetes, Optical coherence tomography

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INTRODUCTION

Diabetes is a significant risk factor for the development of non-arteritic anterior ischemic optic neuropathy (NAION). NOIA-NA can cause irreversible vision loss and is one of the acquired vascular complications affecting the quality of life of patients with diabetes. The prevalence remains high in less advantaged populations and in developing countries, due mainly to a lack of resources. It usually occurs in people over 50 years of age, with an estimated annual incidence of 2.3 to 10.3 per 100,000 people in the USA [1]. The role of diabetes in ischemic damage to small vessels is well known. Arteriosclerosis has been implicated in the pathogenesis of NOIA-NA, although there

is no histopathological confirmation. The pathophysiology has been the subject of much controversy and is still debated [2].

Patients usually present with an acute, unilateral, painless visual decline that may progress over a few days. There is a relative afferent pupillary deficit homolateral to the decrease in visual acuity, indicating optic nerve damage. On the affected side of the eye, there is sectorial or diffuse papilledema, often accompanied by flaming peripapillary haemorrhages.

Recent technologies for optic nerve exploration have attracted the interest of many researchers, as these diagnostic modalities can easily provide information about NOI-NA at any stage of the disease, including optical coherence tomography, which can be a useful tool in neuro-ophthalmology, although its applications in this field have been more limited to date. In optic neuritis, CGC analysis provides more accurate information than RNFLp and serves as an early structural indicator of irreversible neuronal loss [3,4]. Similar to optic neuritis, CGC thickness analysis can detect structural changes masked by acute RNFLp analysis in NOIA-NA [5,6] and be considered an early biomarker of persistent visual impairment.

The aim of the present study is to evaluate tomographic changes in CGC in diabetic patients with NOIA-NA over a 6-month period and to investigate possible correlations with CVAM and DM.

MATERIALS AND METHODS

This is a prospective observational study, conducted at the diabetes reference centre between January 2017 and January 2020. The study adhered to the principles of the Declaration of Helsinki and was approved by the local ethics committee. Informed consent was obtained from all patients before their inclusion.

The diagnosis of NOIA-NA was based on acute, painless visual impairment, papilledema at the fundus, and visual field deficit related to optic nerve damage. The diagnosis of diabetes in this study was based on available laboratory findings of abnormal fasting blood glucose (>1.26 g/dl) and/or elevated glycated haemoglobin (>6.5%) and reports from the patient's endocrinologist.

However, we excluded

- All patients with a previous diagnosis of Horton's disease or with evidence suggestive of temporal arteritis, such as a history of scalp tenderness, a sedimentation rate ≥ 40 mm/h, or a positive C-reactive protein.
- All patients with vitreous or retinal pathologies that may affect central vision or cause visual field defects (e.g., vitreous haemorrhage or organization, retinal detachment, hereditary vitreoretinal or retinochoroidal diseases).

All patients underwent a complete ophthalmological examination including measurement of best corrected visual acuity (BCVA), Goldmann applanation tonometry, and a careful slit lamp examination (model BQ 900; Haag-Streit, Bern, Switzerland) of the anterior and posterior segments.

Patients underwent standard automated visual field, SITA 24-2 program (Humphrey Field Analyser II, Humphrey-Zeiss Instruments, San Leandro, CA), and optical coherence tomography (TOPCON3D-OCT-Maestro, Tokyo, Japan). The following procedures were used:

- We performed a circular scan of the papilla with a diameter of 3.46 mm centered on the papilla. The thickness of the RNFLp was measured around the entire papilla comprising four quadrants of 90°. The scan was performed three times and the clearest image with the strongest signal was selected. The RNFLp thickness at the four quadrants and the overall mean RNFLp thickness was automatically analyzed using the analysis software supplied with the system.
- The CGC was measured using the "CGC" scan protocol. This protocol covers a 6 × 6 mm rectangular area of the macula, cantered 0.75 mm from the temporal side of the fovea.

Patients were checked at the third and sixth months. At each follow-up visit, MAVC, OCT, and CV were measured.

Changes in MAVC, CV, RNFLp, and CGC were assessed at month three and month six after the initial visit. CVAM was converted to log minimum angle of resolution (logMAR). CGC measurements in the affected eyes were compared to those of a control group.

All statistical analyses were performed using SPSS statistical software (version 18.0; SPSS, Inc., Chicago, IL, USA). Student's t-test was used to compare quantitative variables between affected and control eyes. Pearson's correlation was performed to assess the linear correlation between the variables (mean visual field deviation and visual acuity). Statistical significance was defined as $P<0.05$.

RESULTS

We included 80 eyes of 80 diabetic patients with NOIA-NA, satisfying our inclusion criteria. (The mean age was 60.78 ± 6.88 years with extremes ranging from 40 to 75 years, sex ratio F/H=1.28). During the follow-up period, 75 patients had at least three months of follow-up and 71 patients were followed for six months.

Visual acuity and visual field

At the initial visit, the MAVC was 0.50 ± 0.28 log MAR; after six months of follow-up, it improved to 0.401 ± 0.33 Log MAR with a significant difference between the two visits. The mean change in visual acuity from the initial to last visits was 0.11 logMAR. The CV abnormalities at initial presentation were mainly altitudinal deficits that involved primarily the inferior hemi field (in 50% of cases), followed by diffuse deficits in 38.8% of cases and superior altitudinal deficits in 11.3% of cases. The MD varied from -20.45 to -9.01 dB with a mean ± standard deviation of -14.23 ± 2.47 db. The DR in the inferior hemifield was -8.95 ± 3.18 dB greater than the mean

deviation in the superior hemifield, -5.28 ± 4.09 db. A worsening of 2 decibels (dB) or more was found in 15.49% of cases, while an improvement of 2 dB or more was found in 26.76% of cases; it was stable in 57.74% of cases at the last check (Table 1).

Table 1: The evolution of the VA and the mean deviation at the initial consultation, after 3 months and after 6 months.

	Initial visit	After 3 months	After 6 months	Pa	Pb
CVMA (LogMAR)	0.50 ± 0.28	0.403 ± 0.29	0.401 ± 0.33	0.001	0.767
Mean deviation	-14.23 ± 2.47	-14.60 ± 3.04	-14.90 ± 3.74	0.05	0.372
Superior MD	-5.28 ± 4.09	-5.09 ± 4.45	-5.17 ± 4.33	0.347	0.24
Inferior MD	-8.95 ± 3.18	-9.50 ± 3.52	-9.06 ± 2.84	0.047	0.113
CVMA: best corrected visual acuity; MD: mean deviation					
Pa: Comparison between results of the initial consultation and after 3 months					
Pb: Comparison between results of the consultation after 3 months and after 6 months					

RNFLp thickness

The mean RNFLp thickness was 161.91 ± 14.96 µm in the affected eyes and 94.82 ± 8.72 µm in the control eyes. This represents an average increase in RNFLp thickness of 70.75% compared to the RNFLp thickness in control eyes. In the controls, the mean RNFLp thickness was 75.79 ± 12.44 µm at three months and 74.77 ± 13.10 µm at six months. The RNFLp was significantly thinner between the initial visit and 3 months (161.91 ± 14.96 µm vs. 75.79 ± 12.44 µm P<0.001); however, there was no significant difference between the third- and sixth-months' follow-up (89.54 ± 12.44 µm vs. 88.52 ± 13.10 µm; P=0.62). The mean percentage of RNFLp loss compared to control eyes was 32.6% (37.5 µm) at three months and 37.7% (42.3 µm) at six months.

CGC thickness

The mean CGC thickness was 76.93 ± 2.96 µm and 80.03 ± 1.03 µm in affected and control eyes, respectively (P=0.001). This represents a mean decrease in CGC thickness of 3.87% compared to the CGC thickness of control eyes. The mean CGC thickness in the superior hemifield was 76.92 ± 3.48 µm and 76.94 ± 3.62 in the inferior hemifield, with a significant difference between the two groups. The mean thickness of the CGC was 67.12 ± 3.33 µm at three months in the affected eyes compared to 79.95+/-1.44 µm in the control eyes (p<0.001) and 66.56 ± 3.4 µm at six months in the affected eyes compared to 80.18+/-7.08 µm in the control eyes (p<0.001). The CGC was significantly thinner between the initial visit and three months (76.93 ± 2.96 µm vs. 67.12+/-3.33 µm P<0.001) and significantly thinner between the third-month follow-up and the sixth-month follow-up (67.12+/-3.33 µm vs. 66.56+/-3.4 µm P<0.03). The mean percentage of CGC loss after the acute episode was 12.75% (9.81 µm) at three months and 13.47% (10.37 µm) at six months (Tables 2 and Table 3).

Furthermore, the CGC in the superior hemifield was significantly thinner from the third month of follow-up to 6 months (66.61+/-3.83µm and 66.08+/-3.87µm, respectively; P=0.01). Nevertheless, the CGC in the inferior hemifield was significantly thinner from baseline to month 3 (76.94 ± 3.61µm, 67.63+/-4.33µm, p<0.001), but with no significant difference from month 3 to month 6 (67.63+/-4.33µm, 67.04+/-4.27µm, p=0.11) (Table 2).

CGC at the initial visit was significantly associated with VA (r=-0.682; p<0.001) and DM (r=0.946; p<0.001). Similarly, mean CGC thickness at three- and six-months' follow-up was significantly associated with VA (r=-0.633, p<0.001 at 3 months and r=-0.654, p<0.001 at 6 months) and DM (r=0.877, p<0.001 at 3 months and r=0.811; p<0.001 at 6 months) (Table 4).

Table 2: Comparison of CGC thickness to different controls in affected eyes.

CGC of affected eyes	Initial visit	After 3 months	After 6 months	Pa	Pb
Average thickness of the CGC	76.93 ± 2.96	67.12+/-3.33	66.56+/-3.4	<0.001	0.915
Superior hemifield	76.92 ± 3.48	66.61+/-3.83	66.08+/-3.87	<0.001	0.026
Inferior Hemifield	76.94 ± 3.61	67.63+/-4.33	67.04+/-4.27	0.012	0.116
CCG: The ganglion cell layer					
Pa: Comparison between results of the initial consultation and after 3 months					
Pb: Comparison between results of the consultation after 3 months and after 6 months					

Table 3: Comparison of CGC thickness between affected and control eyes at baseline, 3 and 6 months.

	Initial visit			After 3 months			After 6 months		
	Affected eyes	Control eyes	P	Affected eyes	Control eyes	P	Affected eyes	Control eyes	P
Average CGC	76.93 ± 2.96	80.03+/-1.03	0.001	67.12+/-3.33	79.95+/-1.44	<0.001	66.56+/-3.4	80.18+/-7.08	<0.001
Superior CGC	76.92 ± 3.48	80.38+/-1.04	0.003	66.61+/-3.83	79.4+/-1.47	<0.001	66.08+/-3.87	79.52+/-7.06	<0.001
Inferior CGC	76.94 ± 3.61	80.67+/-1.07	0.016	67.63+/-4.33	80.70+/-1.45	0.002	67.04+/-4.27	80.33+/-7.10	0.007

CCG: The ganglion cell layer

Table 4: Correlation between visual acuity, MD, and mean CGC thickness at each visit in affected eyes.

Variables	Initial visit	After 3 months	After 6 months
CVMA (LogMAR)	-0.682**	-0.633**	-0.654**
MD (dB)	0.946**	0.877**	0.811**

CVMA: Best corrected visual acuity; MD: Mean deviation

MD: Mean deviation; CCG: The ganglion cell layer

P*<0.05

P**<0.01

DISCUSSION

In the most common optic neuropathy, glaucoma, the thinning of the CGC parallels the thinning of the RNFLp and reflects progressive damage and loss of the visual field [7]. Given that approximately 50% of retinal ganglion cells are located in the macular region [8] and that NOI-NA tends to frequently affect the central 10° of the visual field, exploration of the CGC may be useful to detect early structural loss, especially when papilledema is present.

The present study provided relevant data on the measurement of CGC thickness in eyes with NOIA-NA in patients with diabetes. The mean CGC thickness was significantly thinner in affected eyes compared to control eyes at baseline (76.93 ± 2.96 µm and 78.03 ± 1.03 µm, respectively (P=0.001). This represents a mean decrease in CGC thickness of 1.40% compared to control eyes. Compared to the normative OCT baseline, 62.5% of affected eyes showed a thinning of the CGC thickness. In contrast, 100% of the eyes showed RNFLp thickening. The rate of CGC thinning increased over time, such that by the third month, 100% of the eyes with NOIA-NA in our study were classified as abnormal.

A retrospective study by Larrea et al. [5] reported that RNFLp measurements in the acute phase were superior to normal limits in most patients. In contrast, CGC analysis showed values inferior to normal limits at the same time in over 50% of cases. This was in agreement with the results of our study, confirming the early impairment of the CGC in the acute phase. Similarly, Keller et al. [9] and De Dompablo et al. [10] reported an early decrease in CGC thickness after acute NOIA-NA compared to the other eye. The current findings of early CGC damage detected by OCT measurements are consistent with OCT findings in experimental models and histological studies in NOIA-NA showing early ganglion cell loss after the onset of ischemia [11]. Histological analysis showed a decrease in CGC thickness during the first 4 weeks [12]. Consistent with these findings, we demonstrated ganglion cell loss in over half of the eyes with NOI-NA in the acute phase.

This study also provided relevant data on CGC thickness in NOI-NA eyes during follow-up. CGC thickness was significantly thinner in affected eyes compared to control eyes at the baseline visit. There was significant thinning of the CGC at month three and month six compared to the initial visit, probably indicating permanent neuronal loss. However, the thinning of the CGC was minimal after 3 months compared to the reduction in RNFLp thickness that was due to both the loss and the resolution of papilledema.

In the study by Han et al. [13] the mean CGC thickness in the NOI-NA group was similar to that of the control group at 1 week, but then decreased significantly below the control mean over the following three months and remained below the control mean CGC thickness for the remainder of the study period (p<0.001). Therefore, CGC thickness showed a rapid decrease during the first 3 months after initial presentation, and this decrease was irreversible during the first year of the disease. This suggests that degeneration of the GCC may occur earlier than degeneration of the RNFLp, probably due to the loss of dendritic cells.

The ability of CGC thickness analysis to predict visual dysfunction in NOIA-NA is very interesting [5,6]. We found that mean CGC thickness was significantly

associated with VA and DM in both acute and chronic phases, highlighting the predictive potential of CGC thickness. Several investigations have demonstrated the ability of CGC to predict visual outcomes in NOIA-NA. A recent study by Dompablo et al. reported this correlation as early as two weeks after acute NOIA-NA [10]. Similarly, in the study by Han et al. [13] visual acuity was significantly and positively correlated with CGC thickness in the superior hemisphere, inferior hemisphere, and total mean CGC thickness ($r=0.344$, $r=0.245$, $r=0.304$, $p<0.001$). This indicates that ganglion cell function is closely related to visual acuity and CV deficits. Thus, the classic teaching that the altitudinal visual field deficit is characteristic of NOIA-NA can now be extended to CGC.

CONCLUSION

This study indicates that early CGC lesions occur in diabetic patients with NOIA-NA in the acute phase, that these lesions can be accurately measured with OCT, and that the significant correlation between CGC changes and visual field deficits and VA represents an important structure-function relationship and highlights the importance of OCT in the assessment of the functional and structural course of eyes with NOIA-NA.

CONFLICT OF INTEREST

The authors declare that they have no conflicts of interest in relation to this article.

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