Correlation between Retinal Nerve Fiber Layer Thickness Measured by GDx and Visual Field in Nonarteritic Anterior Ischemic Optic Neuropathy: A Comparison with the Contralateral Normal Eye

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Abstract

***Purpose*:** To evaluate the correlations between visual field (VF) defects with retinal nerve fiber layer (RNFL) thickness in nonarteritic anterior ischemic optic neuropathy (NAION) eyes, compare different GDx parameters with the other healthy contralateral eyes, and calculate receiver operating characteristic (ROC) curve for the GDx parameters

***Methods*:** Eighteen patients with unilateral NAION from at least 3 months before were enrolled. Patients' healthy eyes were considered as control. Peripapillary RNFL thickness was measured by GDx using variable corneal compensator (GDx VCC) and VF was tested using a central 24-2 program. The GDx measurements and VF test points were divided into 4 sectors and correlations of measured parameters for each nearly corresponding sector were evaluated. The two groups were compared in terms of RNFL thickness and VF sensitivity. Correlation of RNFL thickness and VF was calculated for each sector and ROC curve and sensitivities at specificity of >90% were calculated for each GDx parameter.

***Results*:** All global and most sectoral GDx parameters were significantly different in affected and normal eyes. Temporal-nasal-superior-inferior-temporal (TSNIT) average, TSNIT standard deviation (SD) and nerve fiber indicator (NFI) were significantly correlated to mean deviation (MD) in NAION group (r=0.463, 0.597, -0.713; P=0.05, <0.01, 0.001 respectively). Most of the superior GDx parameters correlated well with the inferior field MD. Superior maximum had the highest sensitivity at ≥90% specificity at best cut-off point of 0.001 (100%).

***Conclusion*:** Most of GDx parameters were correlated with corresponding VF MD in eyes with NAION. Superior maximum was the most powerful discriminator between NAION and normal eyes.

***Keywords*:** Anterior Ischemic Optic Neuropathy, Mean Deviation, Scanning Laser Polarimetry

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Introduction

Anterior ischemic optic neuropathy (AION) which can occur in arteritic anterior ischemic optic neuropathy (AAION) and nonarteritic anterior ischemic optic neuropathy (NAION) forms is an ischemic condition of the optic nerve head. The ischemia occurs at the level of posterior ciliary arteries. NAION is milder than AAION in terms of degree of ischemia and visual impairment. Complete occlusion of the posterior ciliary arteries does not occur in NAION and transient hypoperfusion or nonperfusion of the optic nerve head is the commonest underlying mechanism; the peripapillary choroid and choroidal watershed zones' blood flow is slow and sluggish, but not occluded[1,2] and usually improves with time.[2] Some risk factors have been implicated in the literature for NAION some of which are ischemic heart disease, hypercholesterolemia, diabetes mellitus,[3] crowded disc characterized by small cup to disc ratio,[1,4] hypotension, possibly arterial hypertension, and any cause of marked intraocular pressure (IOP) rise.[1] NAION presents with sudden painless visual field (VF) loss with or without any change in visual acuity (VA).[5] The optic disc is hyperemic and generally or partially swollen. After resolution of the swelling, optic disc pallor remains as the only clinical indicator of ganglion cell loss; RNFL loss in NAION has been shown histologically though.[5,6] Techniques for measuring peripapillary retinal nerve fiber layer (RNFL) thickness such as scanning laser polarimetry (SLP) and optical coherence tomography (OCT) have been used in a few studies to demonstrate this loss quantitatively[7-10] and compare it to normal eyes; but these studies are not conclusive and also no study has been performed to date to analyze the GDx findings to find the best discriminating parameter of the eyes affected with NAION from normal ones. Moreover some of the previous studies have used GDx with fixed corneal compensator for RNFL thickness analysis, which has been shown to be less discriminating in mild to moderate glaucoma than variable corneal compensator (VCC).[11]

The aim of this study was to evaluate the correlations between VF defects with RNFL thickness as measured by GDx VCC in NAION eyes, compare GDx parameters with the other healthy contralateral eyes, and calculate receiver operating characteristic (ROC) curve for the GDx parameters.

Methods

This study was of observational case control type in which 18 patients (6 men, 9 right eyes) with the diagnosis of unilateral NAION between January 2005 and December 2007 were recruited. They had presented at least 3 months before to Farabi Eye Hospital, Tehran, Iran, with typical signs and symptoms of NAION (such as acute, painless unilateral VF loss with or without reduction of VA; relative afferent pupillary defect in the affected eye; optic disc swelling and superficial hemorrhage at the optic disc border and adjacent retina, or both; and color deficit). None of them had any evidence of giant cell arteritis (for example sudden severe visual loss to the level of hand motion or less; symptoms suggestive of polymyalgia rheumatica; tender nodular temporal artery; ipsilateral headache; jaw claudication; elevated ESR to >50mm/hour and pale swollen disc at presentation), glaucoma, IOP greater than 21 mmHg, other optic neuropathies and retinopathies, or any systemic disease affecting the eyes such as diabetes mellitus. The patients had VA of at least $^{20}/_{60}$ in the affected eye at presentation. The presence and severity of relative afferent pupillary defect was assessed. The healthy contralateral eye with VA of more than $^{20}/_{40}$ was used as control. Tehran University of Medical Sciences has approved the study as compatible with declaration of Helsinki. Written informed consent was obtained.

GDx-variable corneal compensator and visual field assessment

Peripapillary RNFL thickness was assessed quantitatively using GDx-VCC (software version 5.3.1; Carl Zeiss Meditec) which is a modified type of SLP system and measures RNFL thickness based on its birefringence properties (Its details can be found in other articles). GDx gives rise to global (for example temporal-nasal-superior-inferior-temporal [TSNIT] average, TSNIT standard deviation, nerve fiber indicator (NFI), symmetry, maximum modulation, elipse modulation, elipse standard deviation and elipse average) and sectoral parameters (such as superior average, inferior average,

superior ratio, inferior ratio, superior-inferior ratio, superior maximum and inferior maximum).

VF was tested using central 24-2 program of Swedish Interactive Threshold Algorithm (SITA) standard strategy of Humphrey Visual Field Analyzer (Humphrey-Zeiss Instruments, San Leandro, California, USA). Fifty-two test points corresponding to all points of C-24-2 grid except those immediately above and below the optic nerve were grouped to six sectors according to the VF- optic disc map produced by Garway-Heath et al in 2000.[12] Because peripapillary nerve fiber in GDx is divided into four sectors (120º superior, 120º inferior, 70º nasal, 50º temporal), the two superior and two inferior sectors of VF were combined to have a four-segment map, so that the resultant field map could be correlated to the GDx map.

Statistical analysis

Means of the data were compared between the NAION eyes and the contralaterlal healthy eyes (control) with Student's T-test. The correlation was calculated for each sector to measure the amount of correlation between perimetry and GDx. All tests were 2-tailed and a P of <0.05 was considered statistically significant. ROC curve and sensitivities at specificity of >90% were calculated for each GDx parameter.

Results

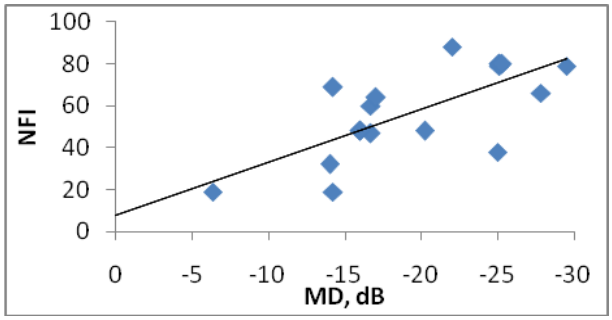
We studied a total of 18 patients with unilateral NAION. The contralateral uninvolved eye was used as control. The mean time between initial examination and study performance was 4.1 months (range, 91-139 days). The mean±standard deviation (SD) age was 61±9.5 years (range, 47-77 years). The mean VA, at the time of study were 0.41±0.35 logMAR (minimum angle of resolution) and 0.10±0.15 logMAR in the affected and control eyes respectively (P=0.002). All affected eyes had optic disc pallor and afferent pupillary defect of 2+ or more. Fourteen of 18 eyes had inferior VF loss, two had superior field defect and in two of them both the hemifields were involved.

Global parameters

The mean±SD of mean deviation (MD) was -19.8±6.13 dB in the affected eyes and -0.62±0.37 dB in the control ones. The difference was statistically significant (P<0.001).

Global GDx parameters were all significantly different between the two groups (Table 1).

As is evident in table 2, TSNIT average, TSNIT SD and NFI significantly correlated with MD in NAION group (Figure 1).



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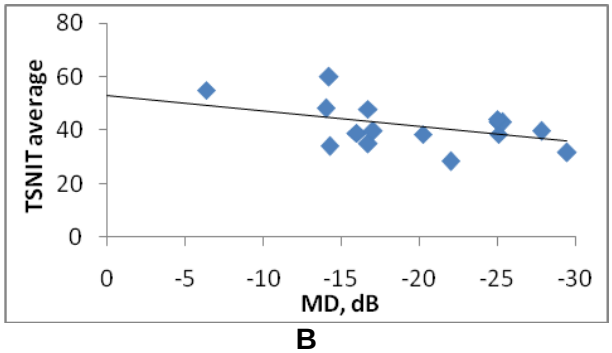

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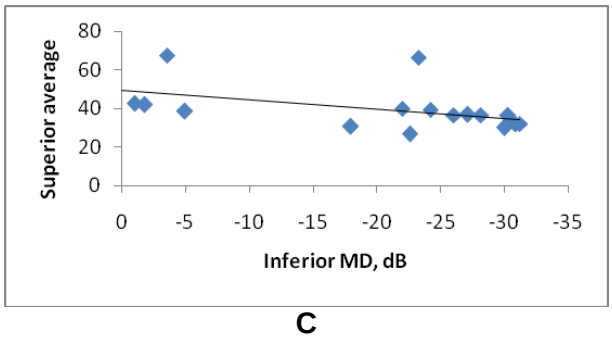

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Figure 1. A) Correlation between visual field mean deviation and GDx global parameter "nerve fiber indicator" in affected eyes (r=-0.713), B) Correlation between visual field mean deviation and GDx global parameter "Temporal-nasal-superior-inferior-temporal average" in affected eyes (r=0.463), C) Correlation between inferior visual field mean deviation and GDx sectoral parameter "superior average" in affected eyes (r=0.473)

Sectoral parameters

All sectoral VF indices in the NAION group were significantly different from those in the control eyes (Table 3).

Most of the sectoral GDx parameters showed decreased RNFL thickness in the NAION eyes compared to normal ones (Table 1).

Table 2 shows the correlation between sectoral GDx parameters with the corresponding VF indices in affected eyes. It is evident that most of the superior SLP parameters correlate well with the inferior field MD, but none of the inferior GDx parameters correlate with the corresponding field sector MD (Figure 1).

ROC curves and sensitivities at specificity of >90% are shown in table 4. The area under curve was ≥0.95 for superior average, superior maximum and normalized superior area with superior maximum having the highest sensitivity at ≥90% specificity at best cut-off point of 0.001 (100%).

Table 1. Global and sectoral scanning laser polarimetry parameters of retinal nerve fiber layer thickness in the nonarteritic anterior ischemic optic neuropathy and normal eyes

	NAION group	Control group	P
Global SLP parameters (mean±SD)			
TSNIT average	41.48±7.77	53.79±4.53	<0.001*
TSNIT SD	13.90±3.34	21.10±5.64	<0.001*
NFI	58.00±21.69	19.50±7.90	<0.001*
Symmetry	0.70±0.20	1.07±0.20	<0.001*
Maximum modulation	1.62±0.88	2.57±0.97	0.005*
Elipse modulation	2.62±0.76	3.69±1.54	0.014*
Sectoral SLP parameters (mean±SD)			
Superior average	38.13±11.30	64.72±7.09	<0.001*
Inferior average	48.09±11.57	61.79±7.20	<0.001*
Superior ratio	1.60±0.65	3.24±1.10	<0.001*
Inferior ratio	2.37±0.85	3.03±0.94	0.15
Superior inferior ratio	1.45±0.39	2.48±1.03	0.08
Superior maximum	45.29±11.77	92.28±12.90	<0.001*
Inferior maximum	64.49±11.78	85.91±11.96	<0.001*
Normalized superior area	0.05±0.03	0.14±0.02	<0.001*
Normalized inferior area	0.09±0.03	0.14±0.03	0.001*

SLP: Scanning laser polarimetry
SD: Standard deviation
TSNIT: Temporal-nasal-superior-inferior-temporal
NFI: Nerve fiber indicator
*: Statistically significant

Table 2. Correlation of global and sectoral visual field mean deviation and global and sectoral GDx parameters in nonarteritic anterior ischemic optic neuropathy eyes

GDx parameter	Correlation coefficient (r) with corresponding MD	P
Global parameters		
TSNIT average	0.463	0.05*
TSNIT SD	0.597	<0.01*
NFI	-0.713	0.001*
Symmetry	-0.119	0.63
Maximum modulation	0.356	0.17
Elipse modulation	0.303	0.22
Sectoral parameters		
Superior average	0.473	0.04*
Superior ratio	0.338	0.17
Superior maximum	0.546	0.01*
Normalized superior area	0.268	0.28
Inferior average	0.336	0.17
Inferior ratio	0.285	0.25
Inferior maximum	0.165	0.51
Normalized inferior area	0.164	0.51

SD: Standard deviation
TSNIT: Temporal-nasal-superior-inferior-temporal
NFI: Nerve fiber indicator
MD: Mean deviation
*: Statistically significant

Table 3. Sectoral visual field mean deviation in the nonarteritic anterior ischemic optic neuropathy and normal groups

Sectoral visual field index	NAION group (mean±SD)	Control group (mean±SD)	P
Superior MD	-11.82±7.18	-.72±0.36	<0.001*
Inferior MD	-21.44±10.89	-6.65±11.22	0.02*

NAION: Nonarteritic anterior ischemic optic neuropathy
SD: Standard deviation
MD: Mean deviation
*: Statistically significant

Table 4. Area under receiver operating characteristic curves and sensitivities at specificity of >90% for GDx parameters

GDx parameter	Area under receiver operating characteristic	P	Sensitivity at ≥90% Specificity (%)	Best cut-off point
NFI	0.93	<0.01	89.9	31
TNSIT average	0.93	<0.01	80.0	0.004
Superior average	0.95	<0.01	60.0	0.003
Inferior average	0.87	0.01	80.0	0.013
TNSIT standard deviation	0.76	0.08	60.0	0.083
symmetry	0.92	<0.01	60.0	0.005
Superior ratio	0.92	<0.01	60.0	0.005
Inferior ratio	0.73	0.11	20.0	0.117
Superior/ Inferior ratio	0.84	0.02	40.0	0.023
Maximal modulation	0.75	0.09	20.0	0.099
Superior maximum	1.00	<0.01	100.0	0.001
Inferior maximum	0.86	0.01	80.0	0.017
Ellipse modulation	0.57	0.62	40.0	0.620
Normalized superior area	0.95	<0.01	60.0	0.003
Normalized inferior area	0.80	0.04	80.0	0.048

TSNIT: Temporal-nasal-superior-inferior-temporal
NFI: Nerve fiber indicator

Discussion

The role of SLP in the diagnosis and management of glaucoma has been widely investigated. Peripapillary RNFL loss measured with GDx VCC has been shown to have a good correlation with VF loss in glaucoma patients[13] and be a good predictor of VF defect development in glaucoma suspect ones[14]; therefore GDx VCC has been suggested as a good tool for follow-up of the patients with mild to moderate glaucoma.[13] There is a better and stronger correlation between sectoral VF indices and GDx parameters than the global ones in glaucomatous eyes.[15] Also GDx VCC parameters have a stronger correlation with VF indices than GDx FCC ones in glaucoma[16,17] and can distinguish early glaucomatous eyes from normal ones more accurately.[11,17]

Some studies have been done to quantitate RNFL loss in nonglaucomatous optic neuropathies. RNFL thickness has been evaluated by SLP in traumatic optic neuropathy,[18] retrobulbar optic neuropathy,[19] central retinal artery occlusion (CRAO)[20] and band atrophy of the optic nerve[21,22] with different success rates.

NAION is diagnosed based on VF defect, which can be quantified by standard automated perimetry (SAP), and optic disc pallor. Optic disc paleness is usually evaluated subjectively by the clinician. Recently, some studied have been performed to quantify optic nerve damage in NAION using SLP or OCT and assess its correlation with VF loss. In the present study, we compared VF and RNFL status of NAION eyes with their normal fellow eyes to see if any difference exists and any correlation can be found between SAP and SLP findings which assess function and structure, respectively. To our knowledge, it is the first one that tries to find the best discriminating GDx parameter between normal and NAION eyes.

In our study, all global GDx parameters showed significant RNFL loss in NAION eyes compared to normal ones. This has been shown in other studies as well.[7]

TSNIT average, TSNIT SD and NFI significantly correlated with MD in NAION group, but maximum modulation and elipse modulation did not. The modulation parameters are measures of global RNFL thickness modulated by patient's own temporal and nasal RNFL as baseline. It can be inferred that NAION eyes had significantly reduced RNFL in all sectors including nasal and temporal ones, so the modulation parameters underestimate this loss and are therefore less correlated with VF MD which is calculated compared to the normal subjects (not the patient's own field). This is in contrast to the study of Danesh-Meyer et al in 2006 in which they stated it might be due to the use of fixed corneal compensator.[7]

Most of inferior and superior RNFL thickness parameters were less in NAION than normal eyes, despite the fact that most of the patients had altitudinal VF defect. However, superior inferior ratio was not significantly different between two groups demonstrating that NAION might cause a generalized ganglion cell loss more prominent in one hemiretina leading to altitudinal field loss.

There was a significant correlation between most of superior RNFL thickness parameters and inferior VF MD, which was the most affected hemifield in the NAION eyes. It should be noted that division of SLP and VF maps into superior and inferior sectors is an arbitrary one and the corresponding sectors of these two maps are not anatomically matched exactly. Therefore it is not surprising that we could not find a significant correlation between all of superior SLP and inferior SAP parameters.

We could not find the "floor effect" described be Schlottman et al in 2004[16] and used by others as a reason for finding a significant correlation between the less affected hemifield MD and corresponding RNFL thickness in NAION eyes.[7,8] Floor effect has been suggested to occur in RNFL measurement with SLP when it is less than 20 µm. Noise from other structures causes an overestimation of RNFL thickness measured with SLP when it is so thin.[7] Our finding might be because mean±SD of RNFL thickness in the superior hemiretina in our patients was 38.13±11.30 µm which is not less than 20 µm.[16]

NFI has been shown to be the best GDx VCC parameter to discriminate between glaucomatous and normal eyes.[23,24] We calculated the area under ROC curve for each global and sectoral GDx parameter, and found that the three parameters, superior average, superior maximum and normalized superior area, had the area under curve of ≥0.95 and superior maximum was the most efficient discriminating one. It should be noted that these parameters are sectoral parameters representing the most prevalent affected hemiretina, in contrast to NFI (for glaucoma) which is a rather global one. This fact is a reflection of more localized nature of neuropathy in NAION than glaucoma, although more studies should be done with larger sample sizes.

The area under curve for GDx parameters in NAION eyes were higher than those for glaucomatous ones reported in other studies.[24-26] This may be due to more severe thinning of RNFL in our cases than glaucoma patients in the studies cited above. Additionally, as RNFL thickness declines with aging,[27] the age difference between normal and glaucoma patients in those studies might account for their lower the area under curve. We enrolled the other healthy eye as control; therefore, the effect of age in our study was eliminated.

Our study, certainly, has several limitations; the sample size is small which may account for some statistically insignificant findings specially in correlations. We do not have a normative database for our own population for VF and SLP parameters and use the Caucasian population values as an alternate. This may account for some different findings we had from others. Inclusion of the other eye as control has one draw-back; the “control” eyes may have had some silent episodes of ischemia which were undiagnosed and this may have affected our observations. Finally GDx is not a very sensitive tool for evaluating nasal and temporal RNFL thickness as is shown in eyes with band atrophy in Monteiro studies[21,22]; therefore we just studied the superior and inferior RNFL parameters.

Conclusion

In conclusion, our study showed that RNFL thickness decreased in NAION compared to contralateral healthy eye. Global and superior GDx parameters significantly correlated with their counterpart VF MD. Superior average, superior maximum and normalized superior area had the highest the area under curve of all GDx parameters. More studies with larger sample sizes are needed in this regard.

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