ORIGINAL ARTICLE

Optic disc topography of normal tension glaucoma patients in Malaysia

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SUMMARY

There are limited data in the literature on the optic disc topography in normal tension glaucoma (NTG) patients in Asian countries, especially in Southeast Asia. This study is aimed at comparing optic disc topography in NTG patients and a control group in Malaysia, and we discuss the literature on NTG studies in other Asian populations. A comparative cross-sectional study was conducted in two hospitals with glaucoma services in Malaysia from November 2010 to February 2012. A total of 109 eyes of 109 Malay patients were included in this study: 32 NTG patients and 77 subjects in the control group. All participants underwent a thorough ocular examination, including visual acuity, subjective refraction, anterior segment and fundus examinations, Humphrey visual field 24-2, intraocular pressure measurement, gonioscopy examination and fundus photography. Optic disc topography was assessed using the Heidelberg Retinal Tomograph III by an identified masked investigator in each hospital. NTG patients had a notably larger disc area (2.65 (0.41) vs 2.19 (0.43) mm^2, respectively), larger cupping (1.54 (0.43) vs 0.63 (0.40) mm^2, respectively), smaller retinal rim areas (1.12 (0.41) vs 1.56 (0.33) mm^2, respectively), higher cup volume (0.47 (0.28) vs 0.11 (0.19) mm^3, respectively), reduced rim volume (0.23 (0.13) vs 0.41 (0.16) mm^3, respectively), higher cup to disc area ratio (0.58 (0.14) vs 0.27 (0.15), respectively), higher linear cup to disc ratio (0.76 (0.09) vs 0.49 (0.17) mm^2, respectively), higher mean cup depth (0.37 (0.09) vs 0.22 (0.09) mm, respectively), higher maximum cup depth (0.77 (0.16) vs 0.59 (0.20) mm, respectively), higher mean of cup shape measure (-0.04 (0.06) vs -0.16 (0.07), respectively), and thinner mean retinal nerve fibre layer thickness (0.15 (0.15) vs 0.24 (0.07) mm, respectively) compared to the control group ($p<0.05$). In conclusion, most of the optic disc parameters were significantly different in NTG patients compared to healthy individuals in Malaysia. Our findings are comparable to those reported in NTG studies in other Asian countries.

KEY WORDS:
Normal tension glaucoma, optic disc topography, Heidelberg Retina Topography III

INTRODUCTION

Normal tension glaucoma (NTG) is a condition with progressive optic nerve damage and visual field loss but normal intraocular pressure (IOP). In clinical practice, it is relatively difficult to differentiate the optic nerve head appearance in NTG patients and those who have physiological cupping. Both entities have a normal anterior chamber angle and range of IOP.

The Heidelberg Retinal Tomograph (HRT) (Heidelberg Engineering, Heidelberg, Germany) is a recent development to combat the above problems, and it has become an objective tool that provides a topographic analysis of the optic nerve head. Numerous studies have described the optic disc topography in NTG patients[1-10].

However, the data available in the literature on optic disc topography in Asians are mainly confined to NTG patients living in Korea[1,9] and Japan[7,8]. Based on a PubMed search, there is no reported study on the optic disc topography of NTG patients from Southeast Asian countries. We aimed to determine and compare the optic disc topography in NTG patients of Malay ethnicity in Malaysia.

MATERIALS AND METHODS

We conducted a prospective comparative cross-sectional study in two glaucoma centres in Malaysia from November 2010 to February 2012. A total of 109 eyes of 109 Malay participants (32 NTG patients and 77 control subjects) were recruited in this study. Approval was obtained from the Research and Ethical Committee, School of Medical Sciences, Universiti Sains Malaysia, and the Ethical Committee of the Ministry of Health, Malaysia. This study protocol adhered to tenets of the Declaration of Helsinki for human research.

We recruited NTG eyes according to the clinical criteria defined by the collaborative normal-tension glaucoma study group in 1998[11]. These criteria included glaucomatous cupping and a corresponding visual field defect, with a median IOP less than 21 mmHg in at least 10 readings and never exceeding 24 mmHg in either eye.

Control subjects were restricted to those without any ocular morbidity, a normal visual field and IOP less than 21 mmHg. Patients were of Malay ethnicity for at least two generations (i.e., all of the parents and grandparents were Malay). Individuals who had mixed marriage in their family pedigree were excluded.

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Exclusion criteria included patients with congenital glaucoma, suspected glaucoma, secondary glaucoma, closed angle, peripheral anterior synechiae, pseudoexfoliation syndrome, angle recession, new vessel at the angle, high myopia with more than - 6.0 diopter, tilted disc, optic disc drusen, dense media opacity, diabetic retinopathy, retinitis pigmentosa, post vitrectomised eyes and amblyopia. Patients with past histories of central nervous system disease or non-glaucomatous optic neuropathy that might interfere with the results were also excluded from the study.

All participants underwent complete ocular examination, including visual acuity, anterior segment and fundus examinations, IOP measurements, gonioscopy, refraction, and fundus photograph documentation. IOP phasing was performed in all NTG patients.

Optic disc cupping was examined by a glaucoma specialist in each centre. A vertical cup disc ratio (VCDR) evaluation was performed based on clinical examination and fundus photographs. The NTG patients were further subcategorised into clinically moderate glaucoma when the VCDR ranged from 0.7 to 0.8 and clinically advanced glaucoma when the VCDR ranged from 0.9 to fully cupped.

All NTG patients and control subjects underwent visual field assessment with the 24-2 program. A reliable visual field was considered only if the false-positive rate was 15% or less, the false-negative rate was 30% or less and the fixation loss was less than 15%. We then sub-categorized NTG patients in both centres according to the Advanced Glaucoma Intervention Study (AGIS) score[12].

The results of visual field assessment with the 24-2 program (SITA standard) were used to determine the AGIS score. The scoring was calculated based on the amount of depression in decibels, which identified the test location as defective on the Humphrey visual field analyser threshold 24-2 test total deviation plot. Mild impairment was considered if the score ranged from 1-5 points, moderate was between 6-11 points, and severe-endstage was considered if the score ranged from 12-20 points.

All participants underwent optic disc topographic analysis using the HRT III by a single identified investigator in both centres. If both eyes were eligible, the parameters of the right eye were selected. Similarly, we included the data for the right eye in the control group.

The image quality was considered to be good according to the criteria described by Bowd et al in 2009[13], which included the optic disc image appearing centrally, minimal eye movement detected during image capture, the absence of artefacts and a topography standard deviation less than 50 micrometres. The optic nerve head images were obtained from a non-dilated pupil.

The data were analysed using computerised Predictive Analytics Software (PASW) Statistics version 18.0. Each parameter was compared between the groups using an independent T-test for continuous variables that were normally distributed, and the Mann-Whitney rank sum test was used for continuous variables that were not normally distributed. A p value <0.05 was considered statistically significant.

RESULTS

We conducted a hospital-based study in two glaucoma centres in Malaysia. The mean age of the NTG group was 64.0 (9.3) years old, with an equal male to female ratio. The mean IOP was significantly lower in the control group. As expected, there were also significant differences of mean deviation (MD) and corrected pattern standard deviation (CPSD) on visual field between the NTG and control groups. The severity of glaucoma was objectively determined based on clinical assessment and the AGIS score. None of our patients had significant myopia that might interfere with the analysis of the optic disc. These data are summarised in Table I.

The comparison of the mean optic disc topography between Malay NTG and control groups is shown in Table II. Our results revealed that NTG patients had significantly larger disc and cup areas, smaller rim areas, increased cup volume, decreased rim volume, a higher cup to disc area ratio, a higher linear cup to disc ratio, increased mean and maximum cup depth, increased mean of cup shape measure, thinner mean RNFL thickness and thinner RNFL cross-sectional areas compared to the control group ($p<0.05$). Height variation contour was the only parameter that did not show a significant difference ($p = 0.855$).

DISCUSSION

There are no large-scale data on the incidence of various types of glaucoma in Malaysia. Selvarajah reported that the incidence of NTG was 0.19% in 68 370 new patients who attended the Eye Clinic, Hospital Kuala Lumpur, Malaysia[14]. Out of 1 966 glaucoma patients, 6.51% were diagnosed with NTG[14]. Malay is the main ethnic group in Malaysia and other Southeast Asian countries, especially Indonesia and Brunei.

Table III highlights the parameters of optic disc topography in our NTG patients and previously published NTG studies[1,7-9] in other Asian countries using HRT analysis. Our study and Shin *et al*[9] analysed optic disc parameters in NTG patients and healthy controls. However, the other three Asian NTG studies[1,7,8] were of a slightly different design, and they were confined to NTG patients only.

Our findings are similar to observations by Shin *et al*[9] from Korea. Except for disc area and height variation contour, those authors reported significant differences in the other optic disc parameters in NTG patients compared to the control group. Shin et al compared the optic disc parameters in 30 normal subjects and 40 NTG and 100 high-tension glaucoma patients who ranged in age from 20 to 75 years using HRT, and they evaluated retinal nerve fibre layer thickness using optical coherence tomography[9].

The two Korean studies[1,9] reported the largest mean disc area (2.70 (0.51) and 2.78 (0.48) mm^2) in their NTG patients. In

Table I: Demographic and clinical characteristics

Characteristics	NTG (n = 32)	Control (n = 77)	p value*
Age (years)			
Mean (SD)	64.0 (9.3)	62.6 (9.2)	0.118
Minimum	45.0	45.0	
Maximum	84.0	84.0	
Gender, n (%)			
Female	16 (50.00)	40 (51.90)	0.850 #
Male	16 (50.00)	37 (48.10)	
Selected eye, n (%)			
Right eye	17 (53.10)	77 (100.00)	0.720#
Left eye	15 (46.90)	0 (0.00)	
IOP			
Mean (SD)	14.8 (3.0)	13.6 (2.9)	0.042
Minimum	11	10	
Maximum	20	20	
Spherical equivalent (D)			
Mean (SD)	-0.55 (1.66)	-0.98 (1.34)	0.363
VCDR, n (%)			
Clinical moderate	18 (56.25)	NA	-
Clinical advanced	14 (43.75)	NA	
MD (dB)			
Mean (SD)	-0.76 (0.82)	-9.34 (7.38)	<0.001
CPSD (dB)			
Mean (SD)	1.47 (0.26)	6.23 (3.97)	<0.001
AGIS score, n (%)			-
Mild	10 (31.26)	NA	
Moderate	11 (34.37)	NA	
Severe-end stage	11 (34.37)	NA	

*Independent T test was applied, #Pearson Chi-Square was applied, NTG = normal tension glaucoma, SD = standard deviation, D= diopter, MD = mean deviation on visual field, CPSD = corrected pattern standard deviation on visual field, dB = decibels, VCDR = vertical cup to disc ratio, AGIS = Advanced Glaucoma Intervention Study

Table II: Comparison of the mean optic disc topography parameters in Malay NTG and control groups

Optic disc parameters	Mean (SD)		MD (95% CI)	T stat (df)	p value*
	NTG (n = 32)	Control (n = 77)			
Disc area (mm^2)	2.65 (0.41)	2.19 (0.43)	0.47 (0.29,0.65)	5.21 (107)	<0.001
Cup area (mm^2)	1.54 (0.43)	0.62 (0.40)	0.91 (0.74,1.08)	10.70 (107)	<0.001
Rim area (mm^2)	1.12 (0.41)	1.56 (0.33)	-0.44 (-0.59,-0.30)	-5.95 (107)	<0.001
Cup volume (mm^3)	0.47 (0.28)[a]	0.11 (0.19)[a]	-	-7.08[b]	<0.001[c]
Rim volume (mm^3)	0.23 (0.13)	0.41 (0.16)	-0.8 (-0.24,-0.12)	-5.85 (107)	<0.001
Cup/disc area ratio	0.58 (0.14)	0.27 (0.15)	0.31 (0.25,0.37)	9.91 (107)	<0.001
Linear cup/disc ratio	0.76 (0.09)	0.49 (0.17)	0.26 (0.20,0.33)	8.16 (107)	<0.001
Mean cup depth (mm)	0.37 (0.09)	0.22 (0.09)	0.14 (0.11,0.18)	7.48 (107)	<0.001
Maximum cup depth (mm)	0.77 (0.16)	0.59 (0.20)	0.18 (0.10,0.26)	4.57 (107)	<0.001
Cup shape measure	-0.04 (0.06)	-0.16 (0.07)	0.12 (0.09,0.15)	8.63 (107)	<0.001
Height variation contour (mm)	0.39 (0.19)[a]	0.40 (0.14)[a]	-	-70.18[b]	0.855c
Mean RNFL thickness (mm)	0.15 (0.10)	0.24 (0.07)	-0.09 (-0.12,-0.06)	-5.38 (107)	<0.001
RNFL cross sectional area (mm^2)	0.88 (0.60)	1.26 (0.35)	-0.38 (-0.56,-0.20)	-4.17 (107)	<0.001

* Independent t test was applied. a median (Iqr), b Z stat, c Mann Whitney test was applied. NTG= normal tension glaucoma, MD= mean difference, SD= standard deviation, df = degree of freedom, Iqr= interquantile range.

Table III: Comparison of the mean optic disc topography parameters in Malay NTG and control groups

Mean parameters (SD)	Current study (2013) Malaysia		Yang and Park (1997) Korea	Shin et al (2008) Korea		Kiriyama et al (2003) Japan	Nakatsue et al (2004) Japan
Group	NTG	Control	NTG	NTG	Control	NTG	NTG
Number of subject, n	32	77	20	40	30	23	60
Disc area (mm2)	2.65 (0.41)	2.19 (0.43)	2.70 (0.51)	2.78 (0.48)	2.48 (0.58)	2.33 (0.48)	2.41 (0.70)
Cup area (mm2)	1.54 (0.43)	0.62 (0.40)	NA	1.51 (0.46)	0.73 (0.39)	1.46 (0.58)	1.34 (0.59)
Rim area (mm2)	1.12 (0.41)	1.56 (0.33)	1.15 (0.27)	1.27 (0.28)	1.74 (0.47)	0.82 (0.21)	1.06 (0.38)
Cup volume (mm3)	0.47 (0.28)	0.11 (0.19)	0.53 (0.33)	0.47 (0.22)	0.17 (0.71)	0.51 (0.35)	0.38 (0.25)
Rim volume (mm3)	0.23 (0.13)	0.41 (0.16)	-	0.27 (0.09)	0.43 (0.09)	0.18 (0.10)	0.23 (0.12)
Cup/disc area ratio	0.58 (0.14)	0.27 (0.15)	0.56 (0.12)	0.53 (0.10)	0.29 (0.14)	0.63 (0.12)	0.54 (0.15)
Mean cup depth (mm)	0.37 (0.09)	0.22 (0.09)	0.37 (0.13)	0.36 (0.10)	0.23 (0.11)	0.38 (0.13)	-
Maximum cup depth (mm)	0.77 (0.16)	0.59 (0.20)	0.76 (0.19)	0.77 (0.20)	0.58 (0.21)	0.81 (0.22)	-
Cup shape measure	-0.04 (0.06)	-0.16 (0.07)	-0.04 (0.09)	-0.06 (0.08)	-0.16 (0.07)	-0.06 (0.05)	-0.06 (0.07)
Height variation contour (mm)	0.39 (0.19)	0.40 (0.14)	-	0.34 (0.11)	0.37 (0.09)	0.42 (0.16)	0.41 (0.14)
Mean RNFL thickness (mm)	0.15 (0.10)	0.24 (0.07)	-	0.19 (0.07)	0.25 (0.08)	0.16 (0.08)	-
RNFL cross sectional area (mm2)	0.88 (0.60)	1.26 (0.35)	-	1.12 (0.40)	1.36 (0.35)	0.83 (0.41)	-

NTG = normal tension glaucoma, SD = standard deviation, RNFL = retinal nerve fiber layer, NA = not available

contrast, the smallest mean disc area was observed in Japanese studies[7,8] (2.33 (0.48) and 2.41 (0.70) mm^2, respectively). The mean disc area in our NTG patients was between these ranges but relatively closer to the Korean data. We believe that genetic differences may contribute to this observation.

It is alarming to note that our NTG patients displayed the largest mean cup area (1.54 (0.43) mm^2), followed by the Korean study published by Shin *et al*[9]. A similar trend was observed for the mean cup area. Both Japanese studies[7,8] reported the smallest mean cup values (1.46 (0.58) and 1.34 (0.59)) in their NTG patients. However, Yang and Park[1] from Korea did not mention this value in their study. It is important to highlight this observation to the ophthalmologists in our region. The over-diagnosis of NTG is likely to occur in clinical practice, especially when there is limited access to visual field and optic nerve imaging analysis. Clinical correlation and the above tests would complement the diagnosis of NTG.

More interestingly, we noted that the values of cup volume, cup to disc ratio, cup depth and shape measurement in our NTG patients were in agreement with other NTG studies in Asian populations[1,7-9]. This observation suggests that these parameters are consistent and useful to denote the structural damage of the optic disc in NTG patients.

The mean RNFL thickness in our patients was also comparable to data reported by Kiriyama *et al*[7]. However, Shin *et al*[9] reported a slightly thicker value in their study. The remaining two studies[1,8] did not specify these data in their reports.

Our study reports the first optic disc topography analysis in NTG patients of Malay ethnicity from Southeast Asia. Our criteria were slightly different compared to the other published NTG studies in Asia. The mean age in our study was relatively higher (64.0 (9.34) years) compared to the other studies[1,7-9] discussed above. Second, we described the severity of the disease in the NTG group based on the clinical assessment of the cup to disc ratio, visual field indices and evaluation of the AGIS score. The severity of glaucoma was described based on visual field indices only in the other published studies[1,7-9]. Third, we believe that differences in the genetic population may play a role.

Some studies reported a significant relationship between age[15-16], gender[17-18] and/or refractive status[15,16,19] and optic disc size, while others described no such relationship[17,20-21]. No significant differences in age, gender, laterality or refractive status were documented in our recruited patients in either group. Our NTG patients comprised an adequate number of moderate and severe types according to clinical assessment and AGIS score.

CONCLUSION

Most optic disc topography parameters are significantly different in NTG patients compared to healthy individuals in Malaysia. Our NTG patients of Malay ethnicity have larger disc and cup areas. It is important to alert ophthalmologists of this new knowledge to avoid the over-diagnosis of NTG. The mean cup volume, cup to disc ratio, cup depth and shape measurement in our NTG patients are consistent with other reported NTG studies in Asian countries, particularly Japan and Korea.

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