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ORIGINAL ARTICLE

The Relationship between Intraocular Pressure and Estimated Intracranial Pressure in Patients with Normal Tension Glaucoma

SYAMIL MS[2], RONA AN[1], JEMAIMA CH[1]

[1]*Department of Ophthalmology, Faculty of Medicine, Universiti Kebangsaan Malaysia, Jalan Yaacob Latif, Bandar Tun Razak, 56000, Kuala Lumpur, Malaysia*
[2]*Department of Ophthalmology, Medical and Health Science Faculty, Universiti Putra Malaysia, 43000 Serdang, Selangor, Malaysia*

ABSTRAK

Kajian ini adalah bertujuan untuk menentukan hubungkait antara tekanan intrakranium (ICP) dan tekanan dalam mata (IOP) pada pesakit tekanan glaukoma normal (NTG) yang sedang menerima rawatan anti-glaukoma melalui formulasi teranggar ICP (estICP) dan perbezaan tekanan translaminar (estTCP). Kajian keratan rentas ini terdiri daripada 66 subjek yang dibahagikan kepada dua kumpulan iaitu kumpulan NTG (33 subjek) serta kumpulan normal (33 subjek) dan telah dijalankan sepanjang 1 November 2017 sehingga 31 Mei 2020 di sebuah hospital tertier di Malaysia. Setelah mendapatkan persetujuan, subjek diperiksa dan seterusnya data yang direkodkan termasuklah tahap tekanan dalam mata, tekanan darah, serta indeks jisim badan (BMI). Ujian lain yang turut dijalankan termasuklah ujian medan penglihatan Humphrey, panjang bola mata, ketebalan sentral kornea (CCT), serta evaluasi terhadap lapisan kepala saraf optik dan makula menggunakan mesin 'Optical Coherence Tomography' (OCT). Anggaran tekanan intrakranium (estICP) dihitung melalui formula; estICP (mmHg) = 0.44 x BMI (kg/m^2) + 0.16 x tekanan darah diastolik (mmHg) – 0.18 x umur (tahun) – 1.91. Seterusnya, anggaran kecerunan tekanan translamina (estTPD) dihitung dengan IOP - estICP. Keputusan analisa menunjukkan tiada perbezaan signifikan pada estICP antara kumpulan NTG serta normal [perbezaan min (95% CI): 0.37 (-1.39, 2.12), p=0.679]. Perbezaan estTPD antara kumpulan NTG dan normal juga didapati tidak signifikan [perbezaan min (95% CI): -1.24 (-2.95, 0.47), p=0.149]. Pembolehubah yang didapati menjadi signifikan pada model multivariat termasuklah tahap ketajaman penglihatan terbaik setelah dikoreksi (BCVA) (p=0.028), lapisan urat saraf retina (RNFL) (p=0.002), purata ketebalan lapisan makula (p=0.002), serta estTPD (p=0.008). EstTPD juga didapati bersifat mencegah pesakit daripada penyakit NTG, di mana peningkatan

Address for correspondence and reprint requests: Associate Professor Dr. Jemaima Che Hamzah. Department of Ophthalmology, Faculty of Medicine, Universiti Kebangsaan Malaysia, Jalan Yaacob Latif, Bandar Tun Razak, 56000, Kuala Lumpur, Malaysia. Tel: +603-9145 5555 ext 5981/5982 Email: jemaima@ppukm.ukm.edu.my

satu unit estTPD dapat mencegah penyakit NTG sebanyak 26.5% [Adj. OR (95% CI): 0.735 (0.586, 0.922), p=0.008]. Kesimpulannya, tekanan dalam kepala didapati berhubungkait dalam peningkatan tekanan dalam mata. Perbezaaan Tekanan Rentas Lamina (TPD) yang lebih tinggi juga didapati mengurangkan kemungkinan mendapat penyakit NTG.

Keywords: glaukoma, tekanan intrakranium, tekanan dalam mata

ABSTRACT

This study aims to determine the relationship between intracranial pressure (ICP) and intraocular pressure (IOP) in patients with normal-tension glaucoma (NTG) who were already on anti-glaucoma treatment using an estimated ICP (estICP) and translaminar pressure difference (estTPD) formula. A cross-sectional comparative study consisted of 66 subjects (66 eyes) who were divided into NTG (n=33) and normal (n=33) group was conducted from 1st November 2017 until 31st May 2020 at a tertiary hospital in Malaysia. After obtaining consent from subjects, ocular and systemic data including IOP, visual field testing, axial length, central corneal thickness (CCT), peripapillary and macular retinal nerve fibre layer evaluation as well as blood pressure (BP) and body mass index (BMI) were collected. The estICP (mm Hg) was calculated as 0.44 x BMI (kg/m^2) + 0.16 x diastolic blood pressure (mmHg) – 0.18 x age (years) – 1.91. The estTPD was derived from this calculated value, where estTPD (mm Hg) = IOP – estICP. Analysis showed there was no significant difference in estimated ICP between NTG and normal subjects [mean difference (95% CI): 0.37 (-1.39, 2.12), p=0.679]. The difference in estTPD between NTG and normal subjects were found to be statistically insignificant too [mean difference (95% CI): -1.24 (-2.95, 0.47), p=0.149]. The variables significant in multivariate model included best corrected visual acuity (p=0.028), retinal nerve fiber layer (RNFL) (p=0.003), average macular (p=0.002) and estTPD (p=0.008). The EstTPD was found to be protective towards NTG, which the unit increased in estTPD will decreased the odds of having NTG by 26.5% [Adj. OR (95% CI): 0.735 (0.586, 0.922), p=0.008]. In conclusion, ICP was correlated in increased in IOP. A higher TPD may be associated with a lower chance of developing NTG.

Keywords: glaucoma, intracranial pressure, intraocular pressure

INTRODUCTION

Glaucoma is a group of eye diseases that progressively causes optic neuropathy, changes to the optic disc and results in a defective visual field (Anderson et al. 2001). The condition is classified based on the anterior chamber angle, either an open or closed-angle glaucoma. The main and traditional factor in the pathogenesis of glaucoma is thought to be increased of

intraocular pressure (IOP). However, certain patients have demonstrated glaucomatous optic disc and visual field defects but have a normal IOP. These patients were later classified to have normal-tension glaucoma (NTG) (Anderson 2003).

The NTG is hypothesised to be caused by primary dysfunction of the autoregulatory mechanism of the vascular system in the eye or occurs secondary to other systemic disorders, such as multiple sclerosis (Mozaffarieh & Flammer 2009). Additionally, structural injury to the optic nerve head and retina seen in NTG, is caused by hypoxia induced by biochemical factors. These factors include endothelins (ET), vascular endothelial growth factor (VEGF), and matrix metalloproteinases (MMPs), which regulate ocular blood flow (Tezel & Wax 2004; Mozaffarieh & Flammer 2009). Anatomically, the optic nerve head is exposed anteriorly to the IOP, while the intracranial portion of the optic nerve is posteriorly bathed with cerebrospinal fluid (CSF) (Hou et al. 2016).

In recent years, researchers began studying the effects of intracranial pressure (ICP) on the IOP, as the optic nerve is exposed to both opposing pressures. The difference between the IOP and ICP is termed translaminar pressure difference (TPD). This gradient is balanced by the relationship between ICP and IOP (Figure 1). It is postulated that higher IOP and ICP influenced the bowing direction of the lamina cribrosa, causing either destructive or protective effects over the ganglion cell axons (Hou et al. 2016). Posterior compression of the lamina cribrosa would cause damage to the axons of ganglion cells in the optic nerve (Quigley et al. 1981; Fechtner & Weinreb 1994).

Individuals with NTG are thought to have a larger TPD as a result of abnormally decreased CSF pressure. Consequently, NTG becomes persistently progressive and occurs despite IOP being in the range of low teens (Ren et al. 2010; Wang et al. 2012). The disparity in pressure between these two spaces causes alteration in axonal transport, impairment of the lamina

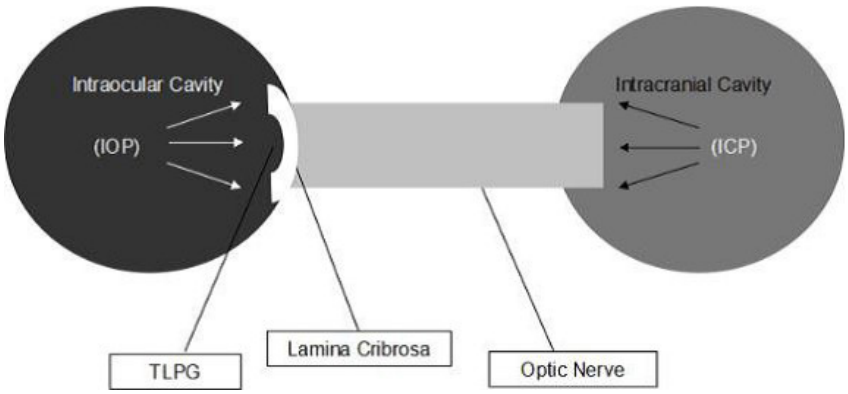

Figure 1: Diagram shows the relationship of pressures affecting optic nerve; intraocular pressure (IOP), intracranial pressure (ICP), and translaminar pressure difference (TPD) (Hou et al. 2016).

cribrosa, or changes in blood flow, ultimately causing the optic nerve to dysfunction (Berdahl et al. 2008). Both primary open-angle glaucoma (POAG) and NTG patients were reported by Berdahl et al. (2008), to have their ICP reduced by 3 to 4 mmHg compared to ocular hypertensive (OHT) subjects.

However, the role of ICP and TPD is still unclear due to limitations in obtaining ICP measurements. Lumbar puncture (LP) and brain ventriculostomy are the gold standard invasive procedures to measure ICP (Morgan et al. 1995). The non-invasive methods include transcranial Doppler, tympanic membrane displacement, and optic nerve sheath diameter readings, which are still under investigation and may not be accurate (Raboel et al. 2012).

Another non-invasive modality uses a formula proposed by Xie et al. (2013) where:
Estimated ICP (estICP) [mmHg] = [(0.44 x BMI [kg/m^2]) + (0.16 x diastolic blood pressure [mmHg])] – [(0.18 x age [Years]) – 1.91]. BMI is body mass index.

The formula is derived through multivariate analysis comparing ICP levels of subjects who underwent LP. Parameters such as age, BMI and blood pressure (BP) were incorporated into the proposed formula due to their association with a higher ICP level. In the study, values generated using the proposed formula were then compared to actual ICP levels. No statistically significant difference was found between the ICP values obtained from the LP and the formula method ($p = 0.29$). The formula-based method also produced similar outcomes in various large population-based studies conducted in China, India, and Korea (Jonas et al. 2013; Wang et al. 2014).

Therefore, to investigate the relationship between ICP and IOP and its risk factors, the formula proposed by Xie et al. (2013) was used for patients with NTG. The analytical approach would possibly help to elucidate the mechanism of glaucoma involving ICP and IOP, to suggest new therapies or management approaches.

MATERIALS AND METHODS

A comparative cross-sectional study was conducted from 1st November 2017 to 31st May 2020 at Hospital Canselor Tuanku Muhriz, Universiti Kebangsaan Malaysia Medical Centre (HCTM, UKMMC). Approval was obtained from the Medical Research and Ethics Committee Universiti Kebangsaan Malaysia (MREC No. JEP-2017-805) and the study was performed according to the Declaration of Helsinki and International Council for Harmonisation (ICH) guidelines for good clinical practice.

Subjects aged 18 and above, with established NTG and undergoing treatment were recruited. Normal control subjects consisted of age-matched healthy relatives of patients attending the HCTM, UKMMC eye clinic and public volunteers with no history of any ocular or systemic disease. Subjects with NTG had open anterior chamber angle, a normal IOP and glaucomatous optic nerve damage with the absence of other known explanations for progressive

glaucomatous optic nerve changes. Exclusion criteria included ocular hypertensive, known hypersensitivity to local anaesthetics, any history of ocular inflammation or infection, had cataract surgery in the less than six months, had undergone other intraocular surgery, phakic intraocular lens (IOL), orbital or ocular trauma, neurological diseases, as well as uncontrolled diabetes mellitus, any condition preventing reliable applanation tonometry, pregnant or nursing women and patients with only one functioning eye.

This study was conducted with a sample size of 33 eyes per group and 80% power to detect a difference in TPD of 3.1 mmHg. Two-sided tests were assumed to control the overall significance level at 5% (PS Power and Sample Size Calculations, version 3.0). Therefore, the study needed 66 subjects.

All subjects were briefed about the study by the investigator (SS) and provided a patient information sheet (PIS). An appointment date was provided for patients who agreed to participate in the study. If both eyes fulfilled the eligibility criteria, the right eye was selected for the study.

During the first visit, the subjects' medical and ocular history were obtained and arterial BP, heart rate (HR) and BMI were measured. The subjects then underwent a full ophthalmic examination consisting of best-corrected visual acuity (BCVA) using the Snellen chart (Hamblin, London, UK), refraction (if subjects were wearing glasses), central corneal thickness (CCT) measurements (Humphrey ATLAS Corneal Topography System, Carl Zeiss, USA), anterior segment examination using the slit lamp biomicroscopy tonometry (Slit lamp BP 900, Haag-Streit, Switzerland), IOP measurement using Goldmann applanation tonometry mounted on the slit lamp biomicroscopy, gonioscopy (Goldmann 3-mirror gonio lens, Volk, USA), optic nerve evaluation using 78D or 90 D (Volk, Ohio, USA), visual fields testing using 24–2 Sita-Standard strategy on Humphrey Field Analyser, Carl Zeiss, USA), peripapillary and macular retinal nerve fibre layer evaluation using spectral domain Optical Coherence Tomography (Spectaralis OCT, California, USA), and axial length measurement using IOLMaster 700 (Carl Zeiss, USA). BCVA measurement with the Snellen Chart was converted into LogMar visual acuity measurements.

The IOP were measured by two researchers (an operator and a reader). The operator was responsible for operating the slit lamp, tonometer and instrument dial, while the reader read and recorded the average of two IOP readings. If measured IOP was more than 2 mmHg, another reading was taken.

The ICP was calculated using the formula by Xie et al. (2013), described in the Introduction section. Estimated translaminar pressure difference (estTPD) (IOP – estICP), was calculated using the resulting value from the formula.

Independent sample t-test identified the difference in estICP and estTPD levels between NTG and normal subjects, while the correlations

between ICP and IOP values were explored using the Pearson correlation test. Logistic regression was used to test the association between risk factors and the development of NTG. Variables with a *p*-value of less than 0.200 in simple logistic regression were included in the variable selection for the multivariate model. Multicollinearity and interaction were checked for the final model. All statistical tests were conducted as two-sided and a *p*-value of less than 0.05 was considered as statistically significant.

RESULTS

Baseline characteristics between NTG and normal subjects were generally similar, except for BCVA, mean deviation (MD) of visual field and nerve fibre layers either of retinal or macula (Table 1). The NTG subjects were found to have poorer BCVA (mean: 0.23 ± 0.17 [6/9] vs. 0.14 ± 0.12 [6/7.5], p=0.011) and lower mean deviation (median [IQR] NTG vs. normal: -4.94 ± 7.28 vs. -3.73 ± 4.42, p=0.03) compared to normal subjects. Normal subjects had significantly higher mean RNFL (NTG vs. normal: 99.82 ± 11.45 vs. 83.94 ± 18.59, p<0.001) but, a significantly lower macular thickness compared to the NTG group (median [IQR] NTG vs. normal: 251.0 + 47.0 vs. 281.0 + 41.0, p=0.002).

There was no significant difference in estICP or estTPD between NTG and normal subjects [mean difference (95% CI: 0.37 (-1.39, 2.12), p=0.679) and (95% CI: -1.24 (-2.95, 0.47), p=0.149)], respectively (Table 2). However, estICP and IOP demonstrated an overall significant moderate positive linear relationship (r=0.388, p=0.001). There was a statistically significant positive correlation between estICP and IOP in NTG subjects (r=0.511, p=0.002), but not in normal subjects (r=0.247, p=0.165), as shown in Figure 2.

The risk factors associated with the presence of NTG were explored using logistic regression. Through this analysis, significant variables consist of

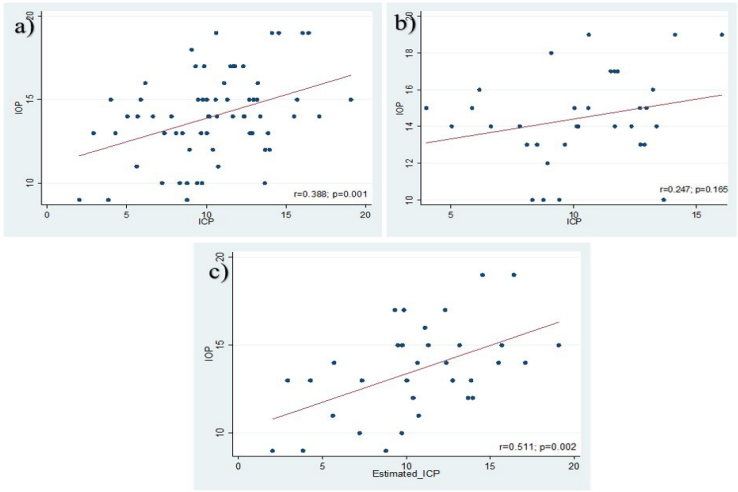

Figure 2: Scatter plot between ICP and IOP for a) all subjects, b) normal subjects and c) NTG subjects

Table 1: Characteristics of the study population

	Overall (n = 66)	NTG (n=33)	Normal (n=33)	p value
Age (years)				
Mean ± SD	65.71 ± 9.88	66.21 ± 11.24	65.21 ± 8.45	0.684[a]
Range	40 - 84	40 - 84	41 - 83	
Gender				
Male	32 (48.5)	18 (56.3)	14 (43.8)	0.325[c]
Female	34 (51.5)	15 (44.1)	19 (55.9)	
Ethnicity				
Malay	27 (40.9)	11 (40.7)	16 (59.3)	0.441[c]
Chinese	29 (43.9)	16 (55.2)	13 (44.8)	
Indian	10 (15.2)	6 (60.0)	4 (40.0)	
Blood pressure (mmHg)				
Systolic, mean ± SD	143.38 ± 20.73	143.55 ± 20.83	143.21 ± 20.96	0.949[a]
Diastolic, mean ± SD	79.32 ± 10.49	80.00 ± 11.66	78.64 ± 9.30	0.601[a]
Heart rate (beats/min)				
Mean ± SD	69.08 ± 10.8	70.00 ± 10.96	68.15 ± 10.80	0.493[a]
Body mass index (kg/m^2)				
Mean ± SD	26.12 ± 4.36	26.49 ± 5.06	25.74 ± 3.56	0.492[a]
Best corrected visual acuity (LogMar)				
Mean ± SD	0.19 ± 0.16	0.23 ± 0.17	0.14 ± 0.12	**0.011**[a]
Intraocular pressure (mmHg)				
Mean ± SD	14.02 ± 2.59	13.58 ± 2.65	14.45 ± 2.49	0.169[a]
Mean Deviation (dB)				
Median (IQR) ± SD	-4.24 ± 5.00	-4.94 ± 7.28	-3.73 ± 4.42	**0.030**[b]
Pattern standard deviation (dB)				
Mean ± SD	3.77 ± 2.76	4.28 ± 3.07	3.26 ± 2.34	0.136[a]
Central cornea thickness (mm)				
Mean ± SD	530.86 ± 35.18	527.12 ± 37.20	534.61 ± 33.17	0.392[a]
Axial length (mm)				
Mean ± SD	24.11 ± 1.47	24.34 ± 1.59	23.89 ± 1.32	0.222[a]
Nerve fibre layer thickness				
Retinal (µm)				
Mean ± SD	91.88 ± 17.28	83.94 ± 18.59	99.82 ± 11.45	**<0.001**[a]
Macular (µm)				
Median (IQR) ± SD	261.0 ± 47.0	281.0 ± 41.0	251.0 ± 47.0	**0.002**[b]

[a] Independent sample t test; [b] Mann Whitney U test; [c] Pearson Chi-square test

Table 2: Comparison between the estimated ICP and TPD level between normal tension glaucoma (NTG) and normal subjects

	NTG	Normal	Mean Difference (95%)	t statistics (df)	p value
Estimated ICP (mmHg) ± SD	10.63 ± 4.19	10.26 ± 2.83	0.37 (-1.39, 2.12)	0.42 (64)	0.679
Estimated TPD (mmHg) ± SD	2.95 ± 3.63	4.19 ± 3.27	-1.24 (-2.95, 0.47)	-1.46 (64)	0.149

*Independent sample t test

BCVA (p=0.017), RNFL (p=0.001) and average macular thickness (p=0.012). Multivariate modelling was further employed to rule out the association, after eliminating confounding effects. Variables which were significant in the multivariate model again were BCVA (p=0.028), RNFL (p=0.002), average macular thickness (p=0.002), with addition of estTPD (p=0.008).

Multivariate analysis (Table 3) showed that a unit increase in BCVA (LogMAR) leads to an increase in the odds of having NTG by 253 times

Table 3: Logistic regression for the risk factors associated with normal tension glaucoma (NTG)

	Simple Logistic Regression			Multiple Logistic Regression		
	OR	**95% CI**	**p value**	**OR**	**95% CI**	**p value**
Age	1.010	0.962, 1.062	0.679			
Gender						
Male	Ref					
Female	0.614	0.232, 1.624	0.326			
Ethnicity						
Malay	Ref					
Chinese	1.790	0.620, 5.170	0.282			
Indian	2.182	0.497, 9.583	0.301			
Systolic blood pressure	1.001	0.978, 1.025	0.948			
Diastolic blood pressure	1.013	0.967, 1.061	0.595			
Heart rate	1.016	0.971, 1.063	0.487			
Body mass index	1.041	0.930, 1.165	0.486			
Best corrected visual acuity (LogMAR)	125.096	2.360, 6631.291	**0.017**	253.048	1.836, 34868.582	**0.028**
Intraocular pressure	0.872	0.717, 1.060	0.170			
Mean deviation	0.900	0.806, 1.005	0.061			
Pattern standard deviation	1.152	0.954, 1.391	0.140			
Central cornea thickness	0.994	0.980, 1.008	0.386			
Axial length	1.241	0.877, 1.757	0.223			
Average RNFL thickness	0.930	0.892, 0.970	**0.001**	0.919	0.871, 0.970	**0.002**
Average macular thickeness	1.018	1.004, 1.032	**0.012**	1.031	1.011, 1.051	**0.002**
Estimated ICP	1.030	0.898, 1.182	0.674			
Estimated TPD	0.899	0.777, 1.039	0.150	0.735	0.586, 0.922	**0.008**

Variable selection forward method used, Nagelkerke R2 = 0.579. Multicollinearity and interaction were checked and not found. Hosmer & Lemenshow goodness of fit test (p = 0.505), classification table = 83.3%, Area under ROC curve = 89.3%

(Adj. OR (95% CI): 253.048 (1.836 - 34868.582), p=0.028). A 10 µm increase in average macular thickness increased the odds of having NTG by 31.0% (Adj. OR (95% CI): 1.031 (1.011 - 1.051), p=0.002). The RNFL thickness and estTPD were individually found to be protective against NTG. An increase of 1 µm in RNFL thickness decreased the odds of having NTG by 8.1% (Adj. OR (95% CI): 0.919 (0.871 - 0.970), p=0.002), while 1 mmHg increase in estTPD decreased the odds by 26.5% of having NTG (Adj. OR (95% CI): 0.735 (0.586-0.922), p=0.008).

DISCUSSION

Lumbar puncture although is a standard method in measuring ICP, is invasive with risks and complications such as infection and haemorrhage. It is a challenge to convince subjects for the procedure without clear clinical indications for study purposes. Therefore, to facilitate studies involving ICP measurements, many non-invasive methods have emerged.

However, these non-invasive methods lack of normative database with levels of ICP vary depending on age, gender and race (Xu et al. 2016), as well as the anatomical location of measurement and position of the body. Routinely, ICP measurement taken from LP may not be equal to the pressure around the optic nerve as the patient lies in a decubital position. Cerebrospinal fluid (CSF) pressure over the retro-orbital area may also differs in volume and anatomical relationship of the ventricles and subarachnoid space surrounding the optic nerve. Thus, the calculated estimated TPD may not be accurate.

The current study used a previously proposed formula by Xie et al. (2013) to estimate ICP in NTG subjects. A statistically significant positive correlation between ICP and IOP was particularly seen in the NTG group. The difference in estICP or estTPD between NTG and normal subjects was statistically insignificant. Multivariate analysis showed that a higher TPD was protective against developing NTG. These findings were contrary to the findings of Jonas et al. (2013) and Lee et al. (2016), which showed that ICP and TPD were lower in NTG patients compared to normal subjects. The study further described that lower ICP and TPD would contribute to the pathogenesis of NTG.

Although Xie et al. (2013) reported no difference between the formula calculation and ICP values obtained from LP and MRI-assisted orbital subarachnoid space width, the formula approach may have contributed to the varied results between the current data and the findings of Jonas et al. (2013) and Lee et al. (2016). Other noted differences were that Xie et al. (2013) used patients only clinically indicated for LP. Moreover, none of them had abnormally high or low ICP and all subjects were of a younger age group with a mean age of 42 $\pm$ 13.4 years old. Both IOP and ICP are dynamic and may follow the diurnal rhythm. Therefore, a one-time measurement of IOP as conducted in this study may not represent the actual pressure but will serve as a preliminary snapshot observation of IOP and ICP

data. Additionally, the dynamics and fluctuations of ICP are poorly understood due to the involvement of complex brain physics, warranting pragmatic and integrative approach with modern brain imaging techniques (Czosnyka et al. 2005). Diurnal IOP and ICP are beneficial in studies that investigates the risks of developing glaucoma.

The CSF is another parameter to consider in NTG. Lindén et al. (2018) found that craniospinal CSF dynamics were not disturbed in NTG subjects. The internal jugular veins of these patients remained intact and did not collapse while in horizontal posture during LP. The study also found that a lower ICP level was seen in the normal control group compared to NTG group. Additionally, visual field defects, IOP, ICP, and TPD in NTG patients were not correlated with body position, whether upright and horizontal. It was postulated that impaired fluid flow between the CSF space and optic nerve subarachnoid space may lead to accumulation of neurotoxins such as β-amyloid, tau, and reactive oxygen species. These toxins are responsible for neuronal damages similar to Alzheimer's disease and normal pressure hydrocephalus. Diminishing CSF flow may cause axonal malnutrition, leading to impaired transport and subsequently death of the retinal ganglion cells.

Igarashi et al. (2019) studied a group of NTG patients with or without idiopathic normal pressure hydrocephalus (iNHP). The data showed that large TPD levels may not necessarily cause further damage to the optic nerve. Additionally, it was found that the NTG group with iNHP had a higher ICP level, shallower optic disc, but a faster rate of glaucoma progression compared to the NTG without iNHP group, although still within a normal range. It was thus hypothesised that decreased CSF turnover or fluctuation of ICP may account for the pathogenesis of NTG in iNHP patients. Therefore, fluctuation of TPD may play an important role in NTG pathogenesis rather than a steady mechanical stress, where intermittent ICP fluctuations with slow and rhythmic oscillation cause more significant effects on cell physiology. The role of ICP in the development of NTG could be determined using studies that investigate the dynamics of CSF.

From another perspective, Hayreh (2009) argued that lamina cribrosa (LC) may not be susceptible to directional bowing as suggested by Berdahl et al. (2008) in describing the pathogenesis of NTG. The LC is a rigid, compact band of connective tissue, anchored firmly to the surrounding sclera and posteriorly to the longitudinal fibrous septa of the optic nerve, with a pressure difference as low as 3-4 mmHg. It is not a free-floating, thin, elastic membrane separating IOP and ICP with mobility. Thus, a rising TPD to as high as 40-60 mmHg, would not cause the posterior bowing of LC that can be opthalmoscopically detected (Hayreh 2009).

However, it is unclear whether LC can be anteriorly displaced if the ICP is on the higher end of the normal spectrum (Berdahl et al. 2008; Hayreh

2008; Hayreh 2009). Berdahl et al. (2008) found that subjects with ocular hypertension (OHT) have higher ICP and TPD compared to other types of glaucoma and control subjects. Higher TPD may have a protective mechanism against the development of glaucoma.

Kim and co-workers (2016) further demonstrated that NTG subjects have a lower lamina cribosa curvature index (LCCI), are deformed less posteriorly in older eyes, and able to maintain normal 'w-shaped' contour of LC compared to the high-tension glaucoma group. Lee et al. (2016) also observed that LCCI may be reduced if the IOP was lowered (i.e. TPD reduced), which may suggest the possibility of anterior bowing of the LC. Berdahl et al. (2012) showed that papilloedema due to intracranial hypertension caused the reduction of TPD and hindered CSF circulation and its surrounding lymphatic drainage, leading to damage of the optic nerve metabolically and hydrostatically. Therefore, increasing TPD encourages retrolamina flow of the CSF that removes putative toxic agents and helps to reverse progression of the disease. New technology in imaging LC and measuring ICP may help to understand the relationship between TPD, ICP and IOP.

Lee et al. (2018) further classified NTG into either steep LC or relatively flat LC groups, based on the LCCI. NTG subjects with a flatter LC had significantly lower baseline IOP, although both groups did not significantly differ in severity. Non-IOP factors were concluded to play a predominant role in this subgroup of NTG patients, which can cause the blockade of axonal transport. In the current study, TPD was found protective against the development of NTG. It is postulated that subjects had a lower LCCI due to anteriorly bowed LC caused by a high ICP. Therefore, raising IOP would widen the TPD and promote CSF flow, which in turn restore homeostatic balance from a pressure gradient, eventually removing damaging neurotoxins. However, further studies are required to more definitively analyse LCCI and the effects of raising the IOP in NTG patients.

In simple logistic regression, BCVA (p=0.017), RNFL (p=0.001), and average macular thickness (p=0.0012) were found to be significant, but in the multivariate model, estimated TPD (p=0.008) was also significantly associated with these factors. Reduction in visual acuity as well as RNFL thickness are inarguably highly associated with NTG progression, leading to visual impairment (AGIS investigators 2002; Mok et al. 2004).

According to our multivariate analysis, thicker macular thickness may increase the risk of developing NTG by 31%. On the contrary, Duan et al. (2010) found reduction of macular nerve fibre layer in glaucoma progression. Thicker central retinal was also found to be associated to the male gender, higher BMI, and longer axial length (Wong et al. 2005). As our study population mainly consisted of males and subjects with higher BMI, they may have been more prone to developing NTG.

Several limitations were highlighted in the present study. Firstly, ICP could

not be measured using the standard LP for comparison purposes. LP was avoided for the current sampled population due to their cultural reservations towards the procedure, based on false beliefs about the complications and side effects of LP. Using non-invasive devices that could measure ICP as good as LP would be ideal for future studies. Secondly, patients in this study had existing glaucoma and were on topical anti-glaucoma medication. Information on the effects of normalisation of IOP with anti-glaucoma medication on ICP and TPD was still unknown. Thus, TPD levels may be altered and not accurately represented. A better representation of TPD in the NTG group in the future, should be performed upon diagnosis to identify the relationship between IOP and ICP. Thirdly, this observational cross-sectional study only provides a general snapshot and may not be a good representative of the true relationship between IOP and ICP. A prospective cohort study may be ideal to determine the effects of TPD on the development of NTG.

CONCLUSION

In conclusion, our study had shown that an increase in ICP was correlated to an increase in IOP. A higher TPD may be associated with a lower chance of developing NTG. However, further studies are required to explore the relationship between IOP and ICP, in the risk of developing NTG. A non-invasive method of measuring ICP equivalent to the standard method would assist in gathering supporting evidence.

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