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REVIEW ARTICLE

Role of Translaminar Pressure Gradient Differences in Glaucoma - A Review

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ABSTRAK

Glaukoma merupakan satu kumpulan penyakit yang merosakkan saraf optik secara berperingkat, lalu mengubah keadaan saraf tersebut serta membuatkan medan penglihatan terjejas. Penyebabnya masih belum jelas sehingga hari ini. Penulis-penulis terdahulu cuba untuk menghubungkaitkan penyakit ini dengan tahap tekanan dalam kepala. Kami menyaring literatur mengenai perkaitan hubungan tekanan dalam mata dan tekanan dalam kepala, di mana ia membawa kepada wujudnya tekanan translamina yang dikatakan menjadi penyebab kepada penyakit ini. Beberapa kajian terdahulu menyatakan bahawa tekanan dalam kepala pada pesakit glaukoma adalah rendah, dan walaupun tekanan dalam mata adalah normal atau tinggi, tekanan translamina akan meningkat. Keadaan ini lalu menyebabkan kerosakan kepada saraf optik di mana ia memberi tekanan ke arah belakang, lantas membawa kepada perubahan glaukoma padanya. Penulisan ini cuba melihat juga kaedah-kaedah terkini dalam mengukur tekanan dalam kepala dengan tepat. Kajian lanjut adalah diperlukan bagi mengukuhkan hubungkait tekanan dalam mata dan juga tekanan dalam kepala pada pesakit glaukoma, seterusnya mengesahkan kajian-kajian terdahulu.

Kata kunci: glaukoma, intrakranium, patofisiologi, tekanan dalam mata, tekanan, translamina

ABSTRACT

Glaucoma is a group of diseases which result in a progressive loss of retinal ganglion cells, producing characteristic optic nerve head appearance with corresponding visual loss. The aetiology remains unclear until today. Previous authors had tried to associate its pathology in relation to intracranial pressure level. We review the

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literature on interrelation of intraocular pressure (IOP) and intracranial pressure (ICP) which gives rise to the study of translaminar pressure gradient (TLPG) in postulating its causal factor towards glaucoma. Several studies had demonstrated that ICP was reduced in patients with glaucoma, and in sequence with normal or raised IOP, leads to increased level of TLPG. The increased TLPG which acts across the lamina cribrosa may cause a posteriorly bowed lamina cribrosa, therefore leading to glaucomatous changes. This review also explores the current available methods in measuring ICP accurately. Further studies are needed to elucidate possible disease mechanism in keeping with IOP-ICP relationship, thus confirming the findings of previous authors.

Keywords: Glaucoma, intracranial, intraocular, pressure, pathophysiology, translaminar

INTRODUCTION

Glaucoma is defined as a group of progressive optic neuropathy which is associated with characteristic visual field defect corresponding to optic disc damage. It can be primary or caused by other diseases. One of the most important risk factor is raised intraocular pressure (IOP) but glaucoma still can occur in patients who have normal IOP leading to exclusion of this component from the current glaucoma definition (American Academy of Ophthalmology 2014). Other risk factors that have been identified associated with glaucoma include advanced age, thin central corneas, large cup-disc ratio (CDR), and a positive family history (Nouri-Mahdavi et al. 2004; Gordon et al. 2002). Of late, few studies have shown that intracranial pressure (ICP) might be an important factor that should be considered in the development of glaucoma, since the optic nerve is bathed by aqueous humor anteriorly and cerebrospinal fluid (CSF) in the subarachnoid space posteriorly (Ruowu et al. 2016). In this review, we examined the current studies exploring the association between ICP and IOP with reference to glaucoma, and attempt to extend our understanding in the pathogenicity of the disease.

PATHOPHYSIOLOGY OF GLAUCOMA

Pathogenesis of glaucoma is still not fully understood until today. Intraocular pressure, which is the only modifiable risk factor, can be within normal range or high in glaucoma and is determined by regulation of aqueous humor production and drainage. Theories regarding pathogenesis of glaucoma are evolving as researchers explore new mechanisms of optic nerve damage (Krakau et al. 1983).

VASCULAR THEORY

Dysfunction of the autoregulatory

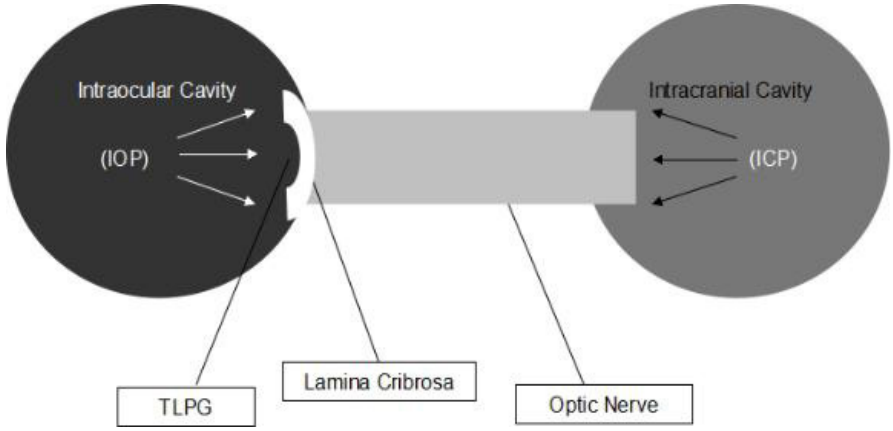

Figure 1: Diagram showing relationship of pressures that affect the optic nerve; intraocular pressure (IOP), intracranial pressure (ICP), and trans-lamina pressure gradient (TLPG) (Ruowu et al. 2016).

mechanism of the ocular circulation has been implicated as the possible pathogenesis for glaucoma. This dysregulatory can occur primarily or caused by other systemic disorders such as Multiple Sclerosis (Flammer et al. 2009). In addition, other mechanism essentially biochemical factors such as Endothelins (ET), Vascular Endothelial Growth Factor (VEGF), and Matrix Metalloproteinases (MMPs) which regulate ocular blood flow might induce hypoxic events in the optic nerve head as well as the retina, resulting in injury to these structures (Tezel & Wax 2004; Flammer et al. 2009).

MECHANICAL THEORY

Anatomical factor of the lamina cribrosa in a pressurized eye may result in compression and distortion from high IOP, which in turn lead to mechanical damage to the retinal ganglion cell axons of the optic nerve. These changes interrupts the retrograde transmission of the neurons to the subsequent visual pathways, and eventually patients progressively develop glaucoma, as shown by optic nerve head changes (Quigley et al. 1981; Fechtner et al 1994).

TRANSLAMINAR PRESSURE GRADIENT

Cranial nerve II, the optic nerve (ON), consists of more than 1 million axons that originate in the ganglion cell layer of the retina and extend toward the occipital cortex. The optic nerve may be divided into the following four topographic areas; intraocular region, intraorbital region, intracanalicular region and intracranial region. Each of these regions have their own pressure conditions. Anteriorly, the ON head is situated in the eye globe, thus exposing it to the IOP which is exerted towards the intraocular walls. Posteriorly, the ON passes through the intracranial cavity to reach optic chiasm. Therefore, there is a pressure inclination across the ON which is the trans-lamina cribrosa pressure gradient

(TLPG) that can be formulated as IOP minus ICP (Figure 1). This gradient is balanced by the relationship between ICP and IOP (Ruowu et al. 2016).

Despite the fact that raised IOP contributes to the development of glaucoma, individuals with normal range of IOP are still at risk for glaucomatous optic neuropathy. In such patients, large TLPG as a result of abnormally decreased CSF pressure is thought to be the cause of this disease to be persistently progressive, despite IOP being in low teens range (Ren et al. 2010; Wang et al. 2012).

The complex interaction of ICP-IOP was further demonstrated microscopically by Wang et al. whereby he investigated the in-vivo effects of this relationship in the microenvironment of the lamina cribrosa itself. He looked into the changes in lamina cribrosa beam thickness as well as its pore diameter with variable level of ICP and IOP, and concluded that the lamina cribrosa deforms with sudden changes in value of both pressures (Wang et al. 2017).

Furthermore, Albon et al. found that the lamina cribrosa also has a decreasing tendency of flexibility towards exerted pressures as the patient ages. This would explain the translaminar pressure gradient being widened in elderly glaucoma patients compared to the younger ones (Albon et al. 2000).

However, the role of TLPG is still unclear due to the limitation of ICP measurements which are currently only available with invasive methods (lumbar puncture or puncture of brain ventricles for patients with severe brain injury) (Morgan et al. 1995).

MEASURING TRANSLAMINAR PRESSURE GRADIENT

Monitoring the ICP is an imperative part in management of diseases, specifically in the discipline of neuromedicine. Various methods are available either invasive or noninvasive. Each methods has its own advantages and disadvantages. A comparative study of these methods by Raboel et al. shown that noninvasive techniques of ICP measurement are more inferior than the invasive techniques, thus deemed unreliable. The gold standard for accurate ICP measurement is by ventriculostomy, however the microtransducer is a noninferior alternative, by which both techniques come with a low risk for hemorrhage and infection. Moreover, zero drift (a difference in ICP value upon starting the measurement when the sensor is calibrated at 0 mmHg, and the ICP value that is measured when the sensor is removed), is a known problem with the microtransducer. Transcranial Doppler, tympanic membrane displacement, optic nerve sheath diameter, CT scan/ MRI and funduscopy are examples of the noninvasive techniques which have been proven to measure ICP inaccurately, even though they bring no risk for invasive methods' complications (Raboel et al. 2012).

Studies were conducted to measure the ICP by taking into account the correlation of ICP-IOP. Lashutka et al. even suggested that abnormal IOP that is measured by handheld tonometry

could indicate an elevated ICP in patients suffering from intracranial lesions (Lashutka et al. 2004).

Nonetheless, Sheeran et al. rebutted the method of using IOP as an indicator of ICP level by which he found that there were a significant inter-patients differences in the ICP-IOP correlation (Sheeran et al. 2000). Czarnik et al. were also in terms of this opinion whereby he found that there were no anatomical and pathophysiological ground to correlate IOP and ICP, and hence the former is not a substitute of the latter (Czarnik et al. 2009). This negative correlation in measurement also consolidated by Muchnok et al. from his pilot study, in which he stated that IOP is not a replacement to assess the ICP, even as a screening tool (Muchnok et al. 2012).

Ideally, clinicians would prefer non-invasive ICP monitoring devices which are cost-effective, readily available, as accurate as the invasive methods, minimal harmless adverse effect and non-operator dependent but none of them match those criteria. Thus, Robba et al. came out with an algorithm of strategically selecting the best non-invasive ICP monitoring devices when certain conditions arises. This guideline is useful for patients who do not meet or contraindicated for invasive procedures of ICP monitoring (Robba et al. 2016). Padayachy also thought that incorporating selected methods of non-invasive devices is a valuableway to increase their efficacy compared to if they were used alone, an approach he described as 'non-invasive multi-modality model' (Padayachy 2016).

Essentially, the challenge of choosing the best non-invasive methods of ICP monitoring rooted from the unavailability of normal database for each devices, considering the wide variety of patients' age, gender, and races across the globe, as narrated by Xu et al. in his review pertaining to this question (Xu et al. 2016).

Recently in 2015, this remark was further scrutinized by Siaudvytyte et al. from Kaunas University giving rise to the study on the role of the two-depth transcranial Doppler based technology which was applied noninvasively on glaucoma patients to measure their ICP. The principle behind ICP measurement in this instrument is based on differences in blood flow of intra- and extracranial segments traversed by the Ophthalmic Artery (OA), which are unequal due to compressive effect of ICP on the intracranial segment of the artery wall. An external pressure (Pe) is produced by a small inflatable ring cuff placed over the tissues surrounding the eyeball. When pressure on the orbit equals the ICP, and flow in the two segments equilibrates, the pressure in the cushion equals the ICP (Pe = ICP), and is expressed in mmHg.More importantly, this method requires no calibration unlike other noninvasive techniques (Siaudvytyte et al. 2015).

RELATIONSHIP BETWEEN TRANSLAMINAR PRESSURE GRADIENT AND INTRAOCULAR PRESSURE IN THE PATIENTS WITH GLAUCOMA

In 2008, Berdahl et al. retrospectively studied the comparison of ICP in subjects with primary open-angle

glaucoma (POAG), normal-tension glaucoma (NTG; subgroup of POAG), and ocular hypertension (OHT) with normal subjects. ICP was found to be reduced in both POAG and NTG as opposed to OHT subjects which had raised ICP. He further concluded that ICP might play a role in the progression of glaucoma in POAG and NTG patients, and on the contrary limiting the conversion of OHT towards POAG.

Berdahl later elaborated that an incongruity between the pressures that affect the optic nerve anteriorly (IOP) and posteriorly (ICP) seems to be an important factor in optic nerve damage, which leads to glaucoma. The pressure disparity between these two chambers, known as the translaminar pressure gradient (TLPG), might cause dysfunction of the optic nerve by cause of alteration in axonal transport, impairment of the lamina cribrosa, or changes in blood flow. Outcome of the study resulted in reduced ICP of 3 to 4 mmHg in POAG subjects as well as its subgroup NTG, upon matching with normal control and OHT subjects. The increased TLPG which acts across the lamina cribrosa may cause a posteriorly bowed lamina cribrosa, therefore leading to glaucoma. Based on the analysed data as well, he reported that by reducing the TLPG, there would be a protective effect against glaucomatous changes of the optic nerve in subjects with OHT who had raised ICP, thus limiting the progression towards glaucoma as a counterbalance effect of the elevated IOP (Berdahl et al. 2008).

In another study by Berdahl et al. in 2012, he reported that starting in the sixth decade of life, there is a 'sustained and significant reduction' of ICP with age especially in females. The age at which ICP began to decrease also coincided with the age when prevelance of glaucoma increased (Fleischman et al. 2012). Additionally, body mass index (BMI), which has been known as a risk factor for POAG, was found to have a positive linear correlation with ICP. This implied that patients with higher BMI may be at a lower risk of developing glaucoma owing to a higher ICP (Berdahl et al. 2012).

Nevertheless, few studies have shown a lack of correlation between ICP and IOP whereby the inherent variability of the correlation between these two parameters reduces its clinical significance. Kirk et al. argued that there was no relationship between ICP and IOP by examining IOP in subjects who were undergoing medically indicated lumbar puncture (LP) (Kirk et al. 2011). The same findings was reported by Han et al. in 2008 when he reviewed data retrospectively from subjects who underwent LP.

Ruowu et al. conducted a study in 2016 to examine the translaminar pressure, and found that all authors whether they agree or disagree with the correlation of ICP-IOP are both partially correct. According to the authors, both pressures are only directly related together in the ICP-IOP dependent zone, unlike in the ICP-IOP independent zone of the gradient in which both pressures started to dissociate from each other. Eight dogs were examined and changes of their ICP and IOP were

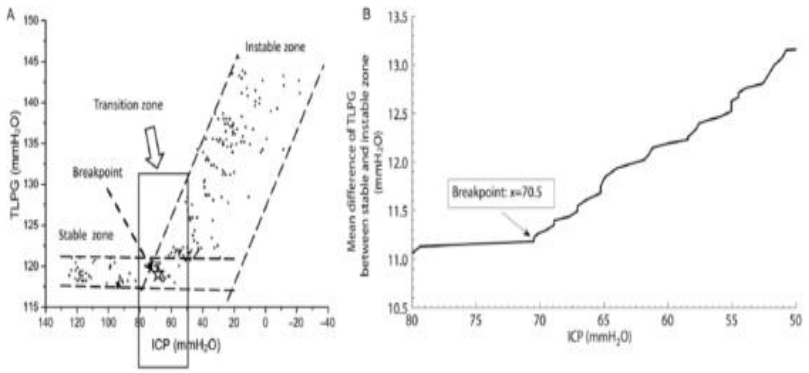

Figure 2: Relationship between ICP and IOP; (A) As ICP increases in the stable zone, TLPG remains almost plateau until ICP reaches 70mm$H_2$0 (breakpoint). However, TLPG widens as the ICP reduces in the instable zone (Ruowu et al. 2016).

recorded. The ICP was artificially lowered through cerebrospinal fluid (CSF) shunting, during which IOP also came down alongside the ICP, and the TLPG remained plateau. This segment is referred as the ICP-IOP dependent zone. Nonetheless, these pressures became dissociated upon reaching a critical value of 70 mmH_2O, which is referred as the ICP-IOP independent zone (Figure 2). This phenomenonresulted in TLPG being linearly escalated through both zones, which might lead to the pathogenesis of various neuro-ophthalmic diseases, including glaucoma (Ruowu et al. 2016).

Another interesting scope of this study which currently becomes the interest of many researchers is the complex relationship of ICP-IOP in various body posture which led them to postulate other factors that might cause glaucoma. Macias et al. studied this correlation in astronauts who came back from space mission complaining of several ophthalmic symptoms and noticed to have signs of ocular diseases. These astronauts showed increased in IOP during head-down tilt posture, but counter balanced by subjecting them to lower body negative pressure. Despite that, this area of study is still far from suggesting a new causal factor for glaucoma (Macias et al. 2015).

FUTURE STUDIES AND CONCLUSION

To date, mounting evidences of relationship between intraocular pressure and intracranial pressure in the development of glaucoma are trending towards its positive correlation. However, it still seems uncertain whether translaminar pressure gradient has been a contributing factor in determining pressure in the optic nerve chamber. Further studies are needed to estimate the level of intracranial pressure in patients with glaucoma and its subtypes in order to establish

a strong causal factor which may lead to optic nerve impairment. Analyses and examination of this phenomenon in a prospective human study, with the advent of the latest technology, would be helpful to elucidate possible disease mechanism, thus confirming the findings of previous authors.

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