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Normal Pressure Glaucoma: The Challenge in Asia and the Scientific Contributions from Asia

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We read with great interest the article in the current issue of *Asia-Pacific Journal of Ophthalmology* by Lee et al[1] reviewing the latest developments in normal pressure glaucoma (NPG). We are particularly interested in the sections on epidemiology, etiologies, causes, and mechanisms. Studies have shown that the percentage of NPG in primary open-angle glaucoma (POAG) varies significantly in different ethnic groups: about 40% in white populations, about 60% in African populations, and about 70% in Asian populations.[1–3] Furthermore, in East Asian populations, it accounts for 83% to 95% of POAG. However, the prevalence of NPG in glaucoma clinics is much lower, indicating that a large majority of such patients remain undiagnosed. A generation ago, NPG was regarded as rare, even by many glaucoma specialists. Increased awareness has brought NPG to the attention of the ophthalmology community, but it requires the realization that elevated intraocular pressure (IOP) is not the only factor in the development of glaucoma, which this review so thoroughly points out. Ophthalmologists need to examine the optic disc and perform visual field examinations, and not just regard patients as not having glaucoma simply because the IOP is in the normal or even low normal range. As many NPG patients may not realize that they have glaucoma or may not be diagnosed until at an advanced stage, they have an increased risk of blindness. Unfortunately, the pathogenesis of NPG remains not fully elucidated, and the mainstay of treatment remains reduction of IOP. With such a high prevalence and the high risk of causing blindness, NPG poses a great challenge in Asia, especially in East Asia. It is not only a challenge of public health concern, but also an important research focus for Asian ophthalmologists. We would like to discuss the recent breakthroughs in the understanding of its possible mechanism and highlight some of the scientific contributions made by Asians.

Intracranial pressure (ICP) and IOP establish a pressure gradient across the lamina cribrosa (LC). Alterations in this translaminar cribrosa pressure difference (TLPD) induce structural changes in the LC, manifested clinically in the forms of optic disc edema or optic disc cupping.[4] The TLPD has been studied in the context of glaucoma and optic disc cupping in animals in both the feline[5] and canine[6] models. However, breakthrough progress for this possible mechanism of glaucoma in human studies was only made in recent years. Berdahl et al from the United States[7] and Wang et al[2] from mainland China,[8] were the first to report that nearly 70% NPG patients had lower ICP. The pressure gradient across the LC increases with elevation of IOP or reduction of ICP. In open-angle glaucoma with normal IOP, ICP is abnormally low, which would lead to an increased transoptic nerve pressure gradient, resulting in progressive optic neuropathy and visual field damage, suggesting that reduced ICP could be a major risk factor for NPG. Apart from lowering the IOP, NPG may also be treated by modulating the ICP.

In a primate study by Wang et al[2] monkeys were implanted with a lumbar-peritoneal cerebrospinal fluid (CSF) shunt, resulting in lowering of ICP. The study found that lower ICP and corresponding increased TLPD were associated with the development of typical glaucomatous optic neuropathy.[9] This is the first primate study to confirm the causal relationship between lower ICP and glaucoma, which provided further insights for the study of optic nerve damage in POAG. The authors reported that if the ICP is too low, CSF would stop flowing from the intracranial subarachnoid space (SAS) into the optic nerve SAS, and CSF drainage from the optic nerve SAS would be interrupted as well, resulting in CSF compartment syndrome.[10,11] Killer et al[12] demonstrated that the optic nerve SAS can become separated from other CSF compartments in certain optic nerve disorders, and they defined this phenomenon as sheath compartment syndrome.[11,13] A decrease in the CSF production rate would reduce the CSF turnover rate, and the decrease in the CSF flow rate may slow the circulation between the posterior optic nerve and CSF, and may even lead to complete

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stoppage of the circulation. This may cause a deficient clearance of toxic substances, which has been known as a contributing factor for the toxicity damage of optic nerve.

Three studies led by Wang et al and Jonas et al, including Handan Eye Study,[2] Beijing Eye Study[14], and Central India Eye and Medical Study,[15] have shown that it is the increase of the pressure gradient caused by increased IOP or decreased ICP may play a role in the pathogenesis of glaucomatous optic nerve damage, rather than increased IOP or decreased ICP per se. Additionally, it has been revealed that both the increase of IOP and the decrease of ICP are associated with the disturbance of both orthograde and retrograde axonal transport.[16] This finding helps to support the possible pathogenesis of glaucomatous optic neuropathy in NPG patients that could not be explained by the traditional mechanical pressure theory and laid a solid theoretical foundation for the proposition of intraocular and intracranial pressure gradient theory.

A cohort study on normal pressure hydrocephalus in Italy demonstrated that after 3 to 10 years of follow-up, 11 of 22 patients with normal pressure hydrocephalus who had undergone ventriculoperitoneal (VP) shunt placement to lower the CSFP developed NPG.[17] This study provided good supporting evidence that low CSFP might be involved in glaucomatous optic neuropathy.

There may be sequelae from long-term abnormal transoptic nerve pressure gradient. Over time, the transoptic nerve pressure gradient could affect axonal transport and microcirculation of the optic nerve, which may aggravate optic nerve damage. This provides new perspectives for research on glaucomatous optic neuropathy and other transoptic nerve pressure gradient-related diseases, such as optic nerve damage with high CSFP and optic neuropathy during space flight. Moreover, if patients have normal transoptic nerve pressure gradient, high ICP would become a protective factor for ocular hypertension patients.

Several studies have revealed that CSFP has a positive, linear relationship with average body mass index (BMI).[18,19] Pasquale et al[19] found that each unit increase in BMI was associated with a 6% reduced risk of glaucoma in women. A similar result was also found in the Handan Eye Study. These findings indicated a direct, linear relationship between CSFP and BMI, and also revealed BMI as one of the most important modifiable risk factors of NPG. For NPG patients with low BMI, nutritional support and physical exercise are recommended; meanwhile, the increase of ICP and the decrease of transoptic nerve pressure gradient could be helpful. Estrogen[20] has also been shown to have a protective effect on the optic nerve. Therefore, postmenopausal NPG patients with low BMI may suffer from accelerated optic nerve damage and visual field progression. Appropriate estrogen supplementation could be recommended for such NPG patients. Systemic vascular diseases are also known as risk factors for NPG and are more common in Asian populations, especially in Japanese and Chinese, which may help explain the high prevalence of NPG in these populations. Hence, routine monitoring of systemic vascular diseases might be a good idea in the routine assessment of patients with NPG in Asia.

Even though the role of TLPD in the pathogenesis of NPG has been demonstrated, it is hard to measure the transoptic nerve pressure gradient in clinical practice noninvasively. To address this issue, Wang et al developed a noninvasive method for the measurement of the trans-optic nerve pressure gradient,[21,22] and the reference range of TLPD (3–8 mm Hg) had been established through study. The new noninvasive method provided a feasible way of measuring TLPD, which could be very useful in diagnosing and monitoring NPG, especially for those with progressive optic neuropathy despite good control of IOP.

The glaucomatous optic nerve damage is not caused by the increase of IOP in NPG, but rather the increase of the transoptic nerve pressure gradient, which leads to a compartment syndrome. Moreover, it is also involved in axonal transport malfunction and altered microcirculation. Further studies that could improve our understanding of the role of CSF around the optic nerve are warranted. At present, lowering IOP remains the mainstay therapeutic approach for the control of transoptic nerve pressure gradient; however, interventions targeting BMI or ICP could be a new direction in NPG treatment. The search for drugs or medical devices useful to NPG by lowering the trans-LC pressure difference and/or by facilitating CSF circulation may be an important area for future research.[23] Although NPG seems to be multifactorial in terms of the etiologies and underlying mechanisms, the abnormal transoptic nerve pressure gradient is likely to be a major one.

A final remark is that Wang et al have made a significant contribution to the development of the transoptic nerve pressure gradient theory as a mechanism of NPG. Together with their noninvasive method in measuring the TLPD, a new and exciting page of NPG research has been opened.

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