

Novel Risk Factors for Glaucoma

Research suggests that many issues other than IOP may play a role in the pathophysiology of glaucoma.

BY SHAN LIN, MD

Although the understanding of glaucoma etiology has improved, the relative role of genetics compared to that of other factors remains elusive. New risk factors—some potentially modifiable—have appeared in the recent literature. This article discusses some of the issues receiving attention in scientific and mainstream publications.

CEREBROSPINAL FLUID PRESSURE

Evidence supports the association of low cerebrospinal fluid (CSF) pressure with the prevalence of glaucoma, particularly with respect to normal-tension glaucoma (NTG). The most robust study comes from Tongren Hospital in Beijing, China, in which patients with both high-tension and normal-tension open-angle glaucoma as well as healthy controls underwent lumbar punctures.¹ Their CSF and translaminar (IOP minus the CSF pressure) pressures were compared. Those diagnosed with NTG had significantly lower CSF pressures than patients with high-tension open-angle glaucoma and control subjects. Furthermore, the translaminar pressure was significantly higher in the NTG group than in the control group.

Although these findings help clinicians to understand the mechanistic aspects of glaucoma's development, the clinical applications are limited because there is no clinically safe method of elevating CSF pressure, even if that were shown to prevent glaucomatous progression.

CALCIUM AND IRON

The human body requires calcium and iron, but these minerals also happen to be oxidants. As a result, when excessive amounts are consumed, these minerals can have toxic effects on various organs.^{2,3} In the eye, calcium and iron may play a role in oxidative stress in retinal ganglion cells as well as in the trabecular meshwork.⁴⁻¹⁰ It is possible that overdoses of calcium or iron can harm the optic nerve and the trabecular meshwork.

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Using data from a US population study, my group found that the highest quintiles of consumption for supplemental calcium and iron were associated with statistically significantly higher rates of self-reported glaucoma (odds ratios of 2.44 and 3.80, respectively).¹¹ In a follow-up study, we found that the risk for glaucoma rose with increasing total consumption of calcium and iron but that it was inversely correlated with adding dietary calcium and iron. This observation suggests that dietary forms of these minerals are safe, whereas supplemental forms appear to be associated with an increased risk. Similar findings have been reported in relation to other disease processes.¹² It should be noted that findings in large population studies do not prove causation but suggest a possible association. One potential confounder in studies related to vitamin and mineral supplementation is that more health-conscious individuals are likely to take such supplements as well as see their doctors for detection of disease.

If our findings are substantiated by other studies, the potential significance may be that clinicians should advise patients with or at risk for glaucoma not to overdo calcium or iron supplementation.

MYOPIA

Growing evidence suggests, the greater the myopia, the higher the risk of developing glaucoma. Several population studies from outside the United States have shown higher hazard ratios for having a diagnosis of glaucoma if myopia is present, particularly high myopia (≥ 6.00 D).^{13,14} Recently, using a large population database representing the US population, my colleagues and I demonstrated an association between high levels of myopia and an increased chance of visual field loss on testing with frequency doubling technology.¹⁵ Although not all cases of visual field loss correspond with glaucoma and may be related to stable optic neuropathy secondary to myopia, this information suggests that there may be more glaucoma suspects among myopes who warrant greater vigilance and follow-up. This risk factor is especially important in certain urban Asian societies in which there is a high rate of myopia¹⁶; in these areas, myopia has become an epidemic.

By the time a patient reaches adulthood, most cases of myopic progression due to axial elongation have stabilized. Future work to decrease the development of myopia, including programs to increase children's time spent outdoors, may help reduce the associated risk for glaucoma.

SLEEP APNEA

Is sleep apnea associated with glaucoma?¹⁷⁻²⁰ Some retrospective or cross-sectional studies have found a positive correlation,^{17,20} but others have not.^{18,19} A recent study from Taiwan used a large population-based database with longitudinal data. The investigators found that a diagnosis of sleep apnea was associated with a higher risk of a subsequent diagnosis of glaucoma over a 5-year period compared to a control group without a diagnosis of sleep apnea.²⁰

If sleep apnea is truly a risk factor for developing glaucoma, then treatment with continuous positive airway pressure or surgery may help to prevent glaucomatous progression. Even if there is no such benefit to treating sleep apnea, therapy may provide a systemic benefit.

BLOOD PRESSURE AND OCULAR PERFUSION PRESSURE

It has been speculated that high blood pressure may be associated with an increased risk for glaucoma. More recent data suggest that low blood pressure and thus low ocular perfusion pressure (blood pressure minus IOP) are correlated with the prevalence and progression of glaucoma.^{21,22}

Recent data from the Barbados Eye Study suggest

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☐ Yes

☐ No

that low ocular systolic, diastolic, and mean perfusion pressures each conferred a twofold greater relative risk for developing glaucoma.²¹ The Early Manifest Glaucoma Trial (EMGT) showed that low ocular systolic perfusion pressure was associated with a 1.42-fold risk for glaucomatous progression.²²

Clinicians can more directly address low blood pressure. If a patient has low blood pressure and NTG, particularly if the low blood pressure is caused by medication, the physician can consider working with the patient's internist to achieve appropriate blood pressure levels without excessive lowering in cases of medicated hypertensive patients. It may be that the bottoming out of blood pressure during the nocturnal period is especially significant to glaucomatous progression, because the IOP is highest during that time. If so, avoiding antihypertensive drugs at night might be helpful.

ROLE OF ESTROGENS

There is ample evidence that estrogen may protect the health of retinal ganglion cells.²³ Late menarche, early menopause, and bilateral oophorectomy have been associated with a higher risk of glaucoma.²⁴⁻²⁶ All of these conditions are tied together by the lower lifetime exposure to estrogen. Recently, investigators found an association between the use of birth control pills and a greater chance of developing glaucoma, likely related to reduced physiological estrogen exposure.²⁷ Another recent study showed that the use of estrogen-only hormone replacement therapy was correlated with a lower risk of developing glaucoma.²⁸

The ophthalmologist has limited influence on patients' exposure to estrogen, but an awareness of the role of estrogen can become a part of risk assessments.

SUMMARY

The novel risk factors presented in this article are not an exhaustive list but rather a sampling of many

issues that may play a role in the pathophysiology of glaucoma. Some may be modifiable, and many deserve further inquiry during a clinical assessment, particularly of patients with NTG in whom high IOP is not the main risk factor. ■

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