REVIEW

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Emerging Concepts in Glaucoma and Review of the Literature

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ABSTRACT

Glaucoma is the most commonly acquired optic neuropathy. It represents a public health challenge because it causes an irreversible blindness. Emerging evidence indicates that the pathogenesis of glaucoma depends on several interacting pathogenetic mechanisms, which include mechanical effects by an increased intraocular pressure, decreased neutrophine-supply, hypoxia, excitotoxicity, oxidative stress, and the involvement of autoimmune processes. In particular, alterations in serum antibody profiles have been described. However, it is still unclear whether the autoantibodies seen in glaucoma are an epiphenomenon or causative. Oxidative stress appears to be a critical factor in the neurodestructive consequences of mitochondrial dysfunction, glial activation response, and uncontrolled activity of the immune system during glaucomatous neurodegeneration. In addition, hearing loss has been identified in association with glaucoma. A higher prevalence of antiphosphatidylserine antibodies of the immunoglobulin G class was seen in normal-tension glaucoma patients with hearing loss in comparison with normal-tension glaucoma patients with normacusis. This finding suggests a similar pathological pathway as a sign for generalized disease.
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KEYWORDS: Antiphospholipid antibodies; Dual sensory loss; Glaucoma; Immune system; Normal-tension glaucoma; Oxidative stress; Retinal ganglion cells

Glaucoma is the second leading cause of blindness globally, after cataracts. It presents an even greater public health challenge than cataracts because the blindness it causes is irreversible.[1] Numerous interesting studies investigate the involvement of immunological mechanisms. Wax et al,[2] in 1998, detected antibodies against endogenous antigens such as heat shock protein 60 in the serum of normal-tension glaucoma patients. Recently, glaucoma patients were found to develop antibody alterations against specific retina and optic nerve proteins.[3] In the experimental autoimmune glaucoma model, Grus and Gramlich[3] demonstrated that an immunization with these proteins causes retinal ganglion cell loss in an autoimmune context. Despite these results, it is still unclear whether the changes in antibody patterns have a causal connection with glaucoma development or are epiphenomena of the disease.[3,4]

TYPES AND SYMPTOMS

Glaucoma is an eye disease that steals vision: the progressive visual field loss typically begins with an arcuate Bjerrum scotoma in the central visual field and ends with total blindness of the eye.[4-7] The demise of retinal ganglion cells is accompanied by morphologic changes of the retina. The cupping of the optic nerve head is the most prominent (**Figures 1 and 2**).

The 2 main types of glaucoma are open-angle and angle-closure. These are marked by an increase in intraocular pressure. Well-marked symptoms are observed only in acute angle-closure glaucoma. All other forms of chronic glaucoma are largely asymptomatic. The only signs are gradually progressive visual field loss and optic nerve

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changes. This is the main reason the disease accomplishes its destruction to a far extent unnoticed. Fifty percent of all patients live without diagnosis until advanced illness.[5]

Normal-tension glaucoma is a form of glaucoma in which damage occurs to the optic nerve without eye pressure exceeding the normal range (12-22 mm Hg).

Secondary glaucoma refers to any form of glaucoma in which there is an identifiable cause of increased eye pressure (traumatic glaucoma, uveitic glaucoma, drug-induced glaucoma, advanced cases of cataract or diabetes, and others).

To diagnose glaucoma caused by autoimmunity, the physician first excludes all other causes of glaucoma.[10]

CLINICAL SIGNIFICANCE

- Glaucoma is a multifactorial optic degenerative neuropathy characterized by loss of retinal ganglion cells. The pathogenesis is a combination of vascular, genetic, anatomical, and immune factors.
- Features are visual field defects until irreversible blindness occurs, cupping of the optic disks, and elevation of intraocular pressure.
- A subset of patients has glaucomatous change despite normal intraocular pressure.
- Hearing disorders can be associated.
- Early detection is the key to protecting the vision.

EPIDEMIOLOGY AND RISK FACTORS

The World Health Organization reports that glaucoma affects approximately 60 million people worldwide.[1] Glaucoma disproportionately affects women and Asians.[11,12] Asian people appear to be at increased risk for angle-closure glaucoma. People of Japanese descent are at higher risk for normal-tension glaucoma. Other high-risk groups include: people over 60 years of age (6 times more likely to get glaucoma), family members of those already diagnosed, steroid users, diabetics, high myopia, hypertension, central corneal thickness <5 mm, and eye injury.

For the year 2020 it is expected that approximately 80 million people will suffer from glaucoma, which is anticipated to result in 11.2 million cases of bilateral blindness.[13,14]

ETIOPATHOGENESIS AND IMMUNE SYSTEM INVOLVEMENT

Glaucoma is a multifactorial optic neuropathy characterized by progressive destruction of retinal ganglion cells and their axons. Müller cells play a key role in the maintenance of retinal ganglion cell bodies in the retina. These specialized macroglial cells are critically important for controlling the extracellular environment, maintaining the extracellular glutamate and ion balance, and buffering oxidative stress.

For decades, a permanent raised intraocular pressure over 21 mm Hg was considered the sole trigger for the onset of glaucoma. However, approximately one-third of all primary open-angle patients did not at any time have a pathologically elevated ocular pressure (normal-tension glaucoma). This raises the question of what, if not the intraocular pressure, is responsible for the destruction of retinal ganglion cells.[15-20]

Apoptosis is accepted as an important component of glaucomatous neurodegeneration.[4,21,22] The initiation of programmed cell death of retinal ganglion cells via tumor suppressor protein p53 and through the activation of the "death receptor" CD95 in autoreactive conditions is documented.[23,24]

Neurotransmitters such as dopamine, serotonin, and glutamate have the potential to drive retinal ganglion cells into programmed cell death. Excitatory mechanisms are

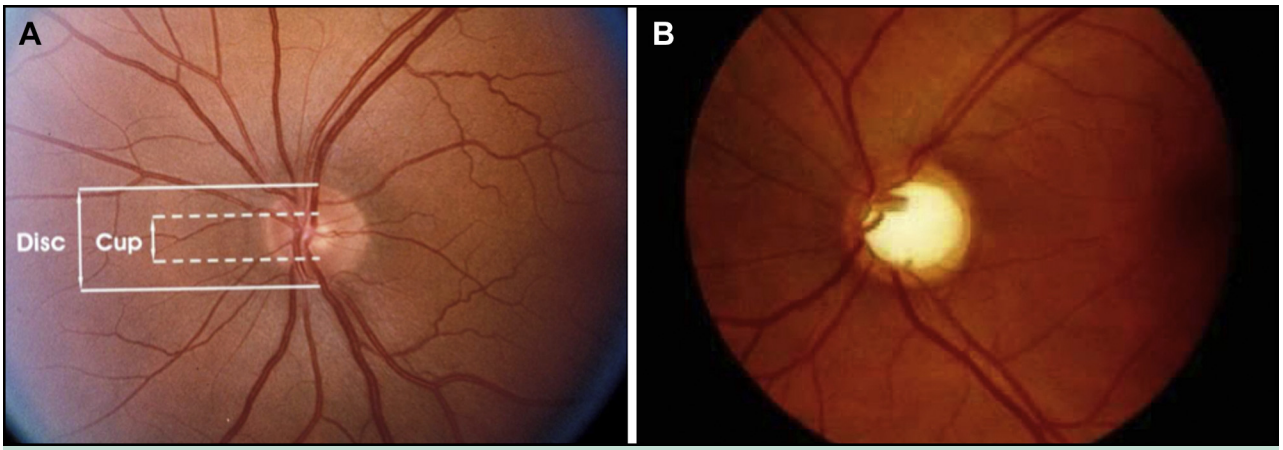

Figure 1 Glaucomatous excavation of the optic nerve: Loss of optic nerve tissue results in excavation or "cupping" of the optic nerve head, which is best viewed by direct ophthalmoscopy. (**A**) Vertical cup-to-disk (C:D) ratio within the normal range. (**B**) Glaucomatous cupping has an increased C:D ratio. From: Adatia FA, Damji KF. *Can Fam Physician*. 2005;51(9):1229-1237.[8]