Glaucoma

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Glaucoma is a heterogeneous group of diseases characterised by cupping of the optic nerve head and visual-field damage. It is the most frequent cause of irreversible blindness worldwide. Progression usually stops if the intraocular pressure is lowered by 30–50% from baseline. Its worldwide age-standardised prevalence in the population aged 40 years or older is about 3·5%. Chronic forms of glaucoma are painless and symptomatic visual-field defects occur late. Early detection by ophthalmological examination is mandatory. Risk factors for primary open-angle glaucoma—the most common form of glaucoma—include older age, elevated intraocular pressure, sub-Saharan African ethnic origin, positive family history, and high myopia. Older age, hyperopia, and east Asian ethnic origin are the main risk factors for primary angle-closure glaucoma. Glaucoma is diagnosed using ophthalmoscopy, tonometry, and perimetry. Treatment to lower intraocular pressure is based on topical drugs, laser therapy, and surgical intervention if other therapeutic modalities fail to prevent progression.

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Introduction

The term glaucoma includes a panoply of diseases that differ in their cause, risk factors, demographics, symptoms, duration, treatment, and prognosis. Glaucoma has become the most frequent cause of irreversible blindness worldwide.[1–3] From a pathophysiological and therapeutic point of view, intraocular pressure is the primary modifiable risk factor, since progression of glaucoma usually stops if this pressure is lowered by 30–50% from baseline. This association suggests that intraocular pressure in glaucoma is too high in relation to the pressure susceptibility of the optic nerve head, at which glaucomatous optic-nerve damage occurs.

The common feature for all forms of glaucoma is loss of retinal ganglion cells, thinning of the retinal nerve fibre layer, and cupping of the optic disc (figure 1; figure 2). According to the morphology of the anterior chamber angle, glaucoma can be divided into open-angle glaucoma and angle-closure glaucoma. The anterior chamber angle contains Schlemm's canal, which is located between the peripheral cornea and the peripheral iris; the aqueous humour leaves the eye through Schlemm's canal (figure 3). In many patients, intraocular pressure (as the most important risk factor for glaucoma) either is increased only slightly or is within the normal range, and the rise in pressure—if present at all—is usually painless. Since chronic glaucoma can progress unnoticed by the patient until central visual acuity and reading ability are affected late in the disease, early detection is important before subjective symptoms develop. In this Seminar, we aim to outline the epidemiology, pathophysiology, symptoms, diagnosis, and treatment of glaucoma, and we discuss potential future developments in this area.

Epidemiology

In 2010, of 32·4 million blind individuals worldwide, glaucoma was the cause of blindness in 2·1 million (6·5%) people.[4] Glaucoma caused visual impairment—defined as visual acuity in the better eye between less than 6/18 and 3/60 or greater—in 4·2 million (2·2%) of 191 million visually impaired individuals worldwide.[4] Because of the association with older age, the overall prevalence of glaucoma was lower in regions with younger populations than in high-income regions with relatively old populations.[4] The global prevalence of glaucoma was roughly 3·5% for people aged 40–80 years.[3] Primary open-angle glaucoma, with a global prevalence of about 3·1%, was six times more common than primary angle-closure glaucoma, which had a global prevalence of about 0·5%.[3] The prevalence of primary open-angle glaucoma was highest in Africa (4·2%), and primary angle-closure glaucoma was most prevalent in Asia (1·1%).[3] In 2013, the number of people aged 40–80 years and affected by glaucoma worldwide was estimated to be 64·3 million, and this number is predicted to increase to 76 million in 2020 and to 112 million in 2040.[3] With respect to primary open-angle glaucoma, men were more likely than women to have this disorder (odds ratio [OR] 1·36), as were people of African ancestry compared with people of European ancestry (OR 2·80).[3] The prevalence of glaucoma-related bilateral blindness was higher in people with primary angle-closure glaucoma than in those with open-angle

Search strategy and selection criteria

We searched the Cochrane library, MEDLINE, and Embase between January, 2000, and December, 2016, with the terms: "glaucoma", "primary open-angle glaucoma", "secondary open-angle glaucoma", "angle-closure glaucoma", "intraocular pressure", "optical coherence tomography", "perimetry", "optic disc", "optic nerve head", "retinal nerve fiber layer", "trabecular meshwork", "glaucoma therapy", and "glaucoma surgery". We largely selected publications from the past 5 years, but we did not exclude commonly referenced and highly regarded older publications. We did not restrict our search by language. We also searched the reference lists of articles identified by this search strategy and selected those we judged relevant. Review articles and book chapters are cited to provide readers with further details and more references than this Seminar has room for. Our reference list was modified on the basis of comments from peer reviewers.

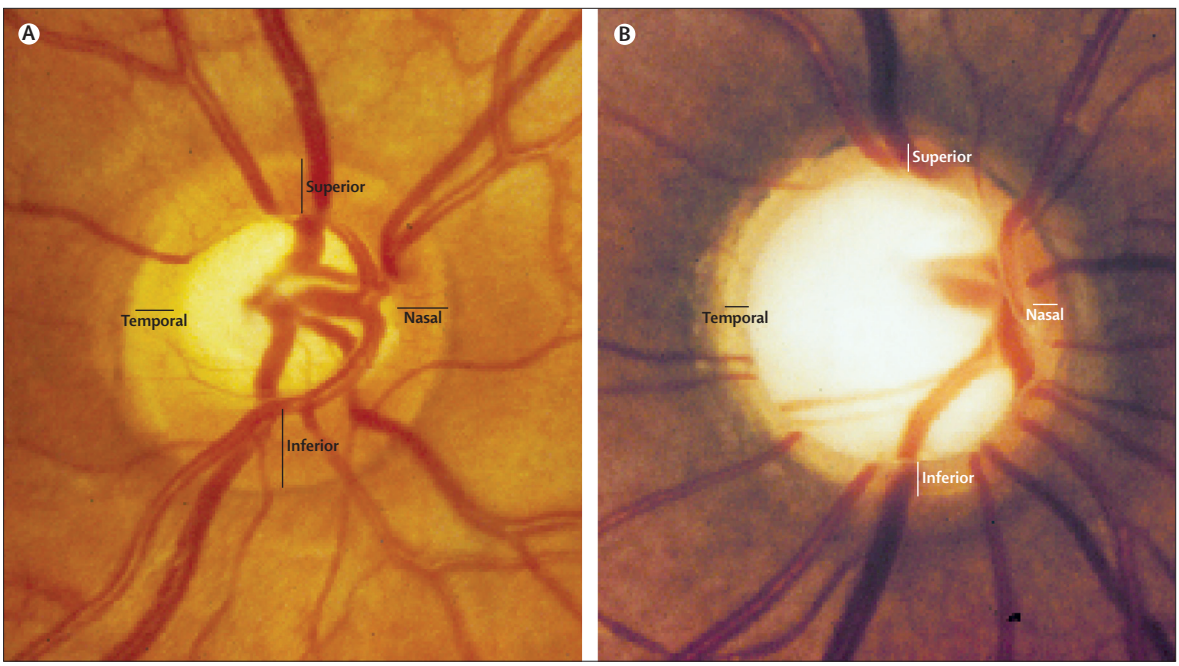

Figure 1: **Ophthalmoscopic photographs of healthy and glaucomatous optic discs**
Photographs were taken of the right eye. (A) In the healthy optic disc, the neuroretinal rim has its normal shape with its widest part in the inferior region, followed by the superior region and the nasal region, and finally the temporal region (referred to as the ISNT rule). (B) In the glaucomatous optic disc, the neuroretinal rim is strikingly thinner than in the healthy optic disc, and the optic cup is subsequently larger, and the cup is deeper.

glaucoma, suggesting that primary angle-closure glaucoma has a worse prognosis.[3]

Anatomy and pathophysiology

Intraocular pressure (normal range 10–21 mm Hg) is regulated by a balance between secretion of aqueous humour by the ciliary body in the posterior chamber and drainage of aqueous humour from the anterior chamber angle, either through the trabecular meshwork and Schlemm's canal or via the uveoscleral outflow pathway through the iris root into the uveoscleral interface (figure 3). Increased intraocular pressure is due to a decreased outflow facility of aqueous humour.

In open-angle glaucoma, the aqueous humour has free access to the trabecular meshwork and Schlemm's canal in the anterior chamber angle. In secondary open-angle glaucoma, the outflow resistance through the trabecular meshwork and Schlemm's canal is increased due to a cause that is detectable by examination of the anterior ocular segment. These conditions include pigmentary glaucoma and exfoliative glaucoma.[5,6] In primary open-angle glaucoma, the anterior chamber angle seems to be unremarkable. The level of intraocular pressure can vary strikingly and could be as low as 10 mm Hg. Optic-nerve damage in primary open-angle glaucoma can develop in the presence of normal levels of intraocular pressure, and this condition has been called normal-pressure glaucoma.[7,8] In such situations, aqueous outflow resistance is normal or might only be slightly increased.

In angle-closure glaucoma, the peripheral iris is in contact with the trabecular meshwork and the peripheral cornea. The peripheral iris blocks the anterior chamber angle so that aqueous humour no longer has access to the outflow system (figure 3). In primary angle-closure glaucoma, the iridocorneal contact is due to forward bulging of the peripheral iris (so-called push mechanism), which is caused by a higher pressure in the posterior chamber behind the iris and a lower pressure in the anterior chamber. The pressure difference is due to increased flow resistance for the aqueous humour through the slit between the iris and lens in association with anatomical abnormalities, such as augmented forward bulging of the anterior lens pole (referred to as anterior lens vault), an enlarged contact area between the posterior iris and the lens surface, and an abnormal insertion of the iris root on the ciliary body.[9–11] The condition is called primary angle-closure glaucoma when the raised intraocular pressure has caused damage to the optic nerve. In secondary angle-closure glaucoma, the iridocorneal contact is caused by the iris being pulled forward (so-called pull mechanism) into the angle because of, for example, neovascularisation in the iris and uveitis. Iris neovascularisation is usually provoked by ischaemic retinopathies such as diabetic retinopathy, with overproduction of vascular endothelial growth factor (referred to as neovascular glaucoma).[12] In congenital glaucoma, the transtrabecular outflow is reduced, often due to an underdeveloped trabecular meshwork and Schlemm's canal.[13] The increase in intraocular pressure

in children younger than 2 years results in enlargement of the globe, also called buphthalmos.

Common to all forms of glaucoma is glaucomatous optic neuropathy, characterised by loss of the neuroretinal rim and widening of the cup in the optic disc (figure 1; figure 2).[14–16] The optic disc (also called the optic nerve head) is located 15° nasally to the fovea (ie, the centre of the macula) and allows the exit of retinal ganglion cell axons from the eye.[17,18] The base of the optic nerve head consists of the lamina cribrosa, a perforated collagenous sieve-like structure through which the optic nerve fibres and blood vessels pass. Damage to optic nerve fibres occurs at the lamina cribrosa (figure 4),[19] which is the frontier between the intraocular compartment and the retro-laminar compartment.[20–22] In eyes with raised intraocular pressure in particular, the increased pressure difference across the lamina cribrosa causes stress and strain on this structure.[23] This pressure difference results in eventual compression, deformation, and remodelling of the lamina cribrosa and impedes orthograde and retrograde axonal transport within the optic-nerve fibres.[19,24–27]

Besides raised intraocular pressure, work is needed to establish whether a low ocular perfusion pressure (the difference between intraocular pressure and systemic blood pressure) might be associated with glaucomatous optic neuropathy.[28–32] Findings of studies have suggested an association between glaucomatous optic-nerve damage and an abnormally low blood pressure at night;[30,31] therefore, drugs that lower blood pressure might be best administered to patients with glaucoma and arterial hypertension in the morning. Studies are needed to investigate whether mitochondria located in high concentrations in the prelamina cribrosa region have a direct role in pathogenesis of glaucomatous optic neuropathy.[33,34] In a similar manner, pathways from gene mutations contributing to glaucoma, and eventual dysfunction of the encoded proteins, have not yet been analysed fully.[35,36]

Glaucoma-associated loss of neurons is not limited to retinal ganglion cells but extends into the lateral geniculate nucleus and the visual cortex.[37–39] Findings of clinical studies and histological investigations have suggested that glaucomatous damage affects all subsets of retinal ganglion cells in a similar manner.[37,38] Study findings also showed that the glaucomatous loss of retinal ganglion cells and their axons was accompanied by changes in the glial cell population, including astrocytes and retinal microglial cells.[40–42]

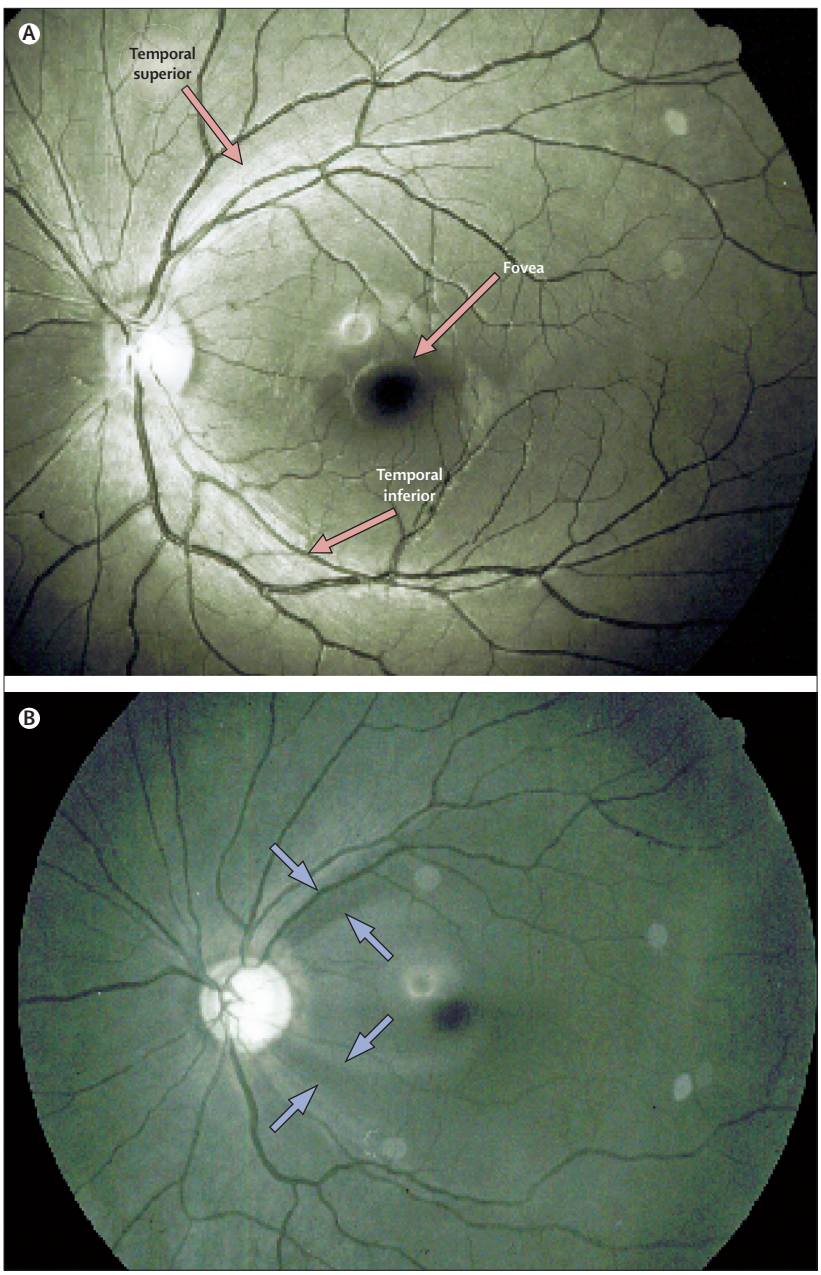

Figure 2: **Ophthalmoscopic photographs of the retinal nerve fibre layer of two different eyes**
(A) The photograph shows a healthy retinal nerve fibre layer. (B) The photograph shows the retinal nerve fibre layer of an eye with glaucomatous optic-nerve damage, with localised retinal nerve fibre layer defects (light blue arrows), in addition to a diffuse diminution of the retinal nerve fibre layer.

Risk factors

The main risk factors for both development and progression of glaucoma are older age,[3,43–46] an intraocular pressure too high in relation to the pressure sensitivity of the optic nerve head,[7,47–51] ethnic background,[44,52] a positive family history for glaucoma, stage of disease, and high myopia.[53–55] Findings of a randomised placebo-controlled trial showed that medical lowering of intraocular pressure resulted in preservation of visual field in patients with open-angle glaucoma.[51] In a meta-analysis of population-based studies, the odds ratio for primary open-angle glaucoma was 1·73 (95% CI 1·63–1·82) for each decade increase in age beyond 40 years.[3] Similarly, the prevalence of primary angle-closure glaucoma increased with older age. Across all ethnic origins, individuals of African ancestry had the highest prevalence of glaucoma (6·11%, 95% CI 3·83–9·13) and primary open-angle glaucoma (5·40%, 3·17–8·27), whereas

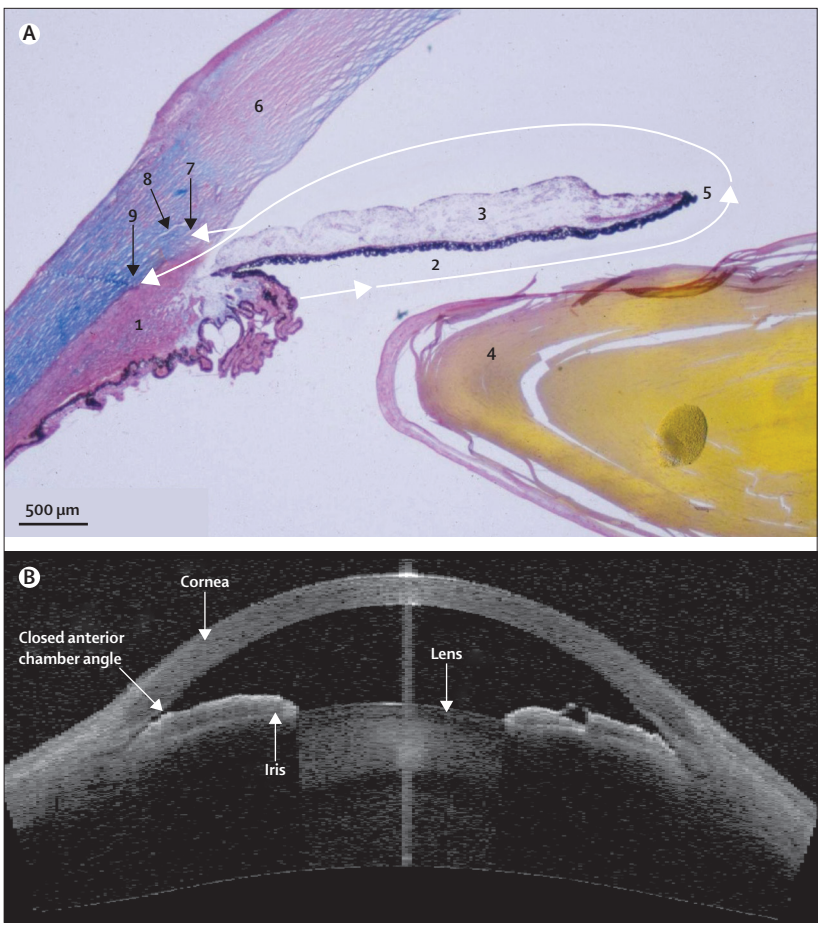

Figure 3: **Imaging of the anterior segment of the eye**
(A) Histophotograph shows the anterior segment of a healthy eye with an open anterior chamber angle, with the ciliary body (1) in the posterior chamber, which is the site of aqueous humour production, and the slit (2) located between the posterior iris surface (3) and the anterior lens surface (4) and functioning as a connecting path for the aqueous humour to percolate (white line) from the posterior chamber into the anterior chamber through the pupil (5). The anterior chamber angle is located between the peripheral cornea (6) and the peripheral iris and contains the trabecular meshwork (7) and Schlemm's canal (8). The aqueous humour leaves the eye through the trabecular meshwork and Schlemm's canal and through the uveoscleral outflow pathway (9). (B) Optical coherence tomogram of the anterior segment of an eye with closed anterior chamber angle.

the Asian population had the highest prevalence of primary angle-closure glaucoma (1·20%, 0·46–2·55).[3] Sex has been associated inconsistently with the prevalence of open-angle glaucoma, yet in two meta-analyses of population-based glaucoma studies, a higher prevalence of primary open-angle glaucoma was reported in men than in women.[3,47] High myopia with a myopic refractive error of roughly more than –8 diopters was another strong risk factor for glaucoma.[53–56] Correspondingly, findings of the Singapore Malay Eye Study showed an association between moderate or high myopia (worse than –4 diopters) and a higher prevalence of primary open-angle glaucoma.[55]

Diagnosis of glaucomatous optic neuropathy can be missed in myopic eyes because intraocular pressure is typically within the normal range and the myopic appearance of the optic nerve head makes detection of glaucomatous changes difficult. Study findings have suggested that the main factor for the myopia-associated increase in glaucoma susceptibility is the myopia-associated enlargement of the optic disc.[56] Secondary stretching and thinning of the lamina cribrosa in association with an elongation and thinning of the parapapillary tissues could lead to pronounced changes in the biomechanics of the optic nerve head and an increase in glaucoma susceptibility. Another factor could be the biomechanics of the optic nerve dura mater, which pulls on the peripapillary sclera in eye movements and increases the stress and strain of the lamina cribrosa.[57]

Socioeconomic status affects early detection of glaucoma and initiation of and adherence to treatment;[58,59] therefore, this factor is associated with prognosis of the disease. Whether nutritional status and diet have an effect on the prevalence and incidence of any form of glaucoma is unclear. The relation between primary open-angle glaucoma and diabetes mellitus,[60,61] arterial hypertension,[62,63] body-mass index,[64] obstructive sleep apnoea,[65] and oral contraceptive use[66] is uncertain. Although controversial, low CSF pressure and low ocular perfusion pressure, including a low systemic blood pressure, might potentially have a role in glaucoma.[22,28–31,67–69]

A thin central cornea has been deemed a risk factor for glaucoma because a thin cornea leads to falsely low measurements of intraocular pressure.[43,70] Furthermore, a thin cornea could be a structural risk factor because of a hypothetical association with a thin lamina cribrosa.[71–73] An association between corneal thickness and thickness of the lamina cribrosa has, however, not been shown yet.[71] Correspondingly, in an east Asian population,[72,73] corneal biomechanical variables—eg, corneal hysteresis and corneal resistance factor—were not correlated with the severity of primary angle-closure glaucoma, nor was central corneal thickness associated with glaucoma.

The main systemic risk factors for development of primary closure of the anterior chamber angle are older age, east Asian ethnic origin, and female sex, in addition to the main ocular risk factor of axial hyperopia. The hyperopic eye has a small anterior chamber, a thick and more anteriorly positioned lens, a thick iris, and greater forward bulging of the anterior lens pole (or anterior lens vault).[9,10,74,75] The reduced space in the anterior chamber leads to a higher risk of a blockage of the anterior chamber angle by peripheral iris tissue in mid-mydriasis. The angle obstruction can occur acutely, leading to acute and painful angle-closure glaucoma, or it might develop chronically, associated with painless chronic angle-closure glaucoma.

Genetics

Based on findings of genome-wide association studies, primary open-angle glaucoma is associated with several genes: *CDKN2B-AS1, CAV1* and *CAV2, TMCO1, ABCA1, AFAP1, GAS7, TXNRD2, ATXN2,* the chromosome 8q22 intergenic region, and *SIX1* and *SIX6*.[36,76–89] In particular, myocilin, optineurin, and *WDR36* are linked to adult glaucoma,[77–79] *CYP1B1* to glaucoma in children and

younger adults,[90] and *LOXL1* to exfoliative glaucoma.[80,81,91,92] This range of loci in primary open-angle glaucoma is unexpectedly broad. Findings of genome-wide association studies have also identified genetic loci associated with quantitative glaucoma-related traits—eg, intraocular pressure, central corneal thickness, and optic disc size.[90,92,93–97] Unexpectedly, the number of genetic loci shared between intraocular pressure and the primary open-angle glaucoma phenotype was small (ie, *CAV1* and *CAV2*, *TMCO1*, *ABCA1*, and *GAS7*), suggesting that genetic susceptibility to primary open-angle glaucoma is not accounted for solely by raised intraocular pressure. Genetic associations of glaucoma vary according to ethnic group. Common glaucoma susceptibility alleles seen in white European populations at the genome-wide level (eg, *CDKN2B-AS1*, *TMCO1*, *CAV1* and *CAV2*, chromosome 8q22 intergenic region, and *SIX1* and *SIX6*) seem to have weaker associations with primary open-angle glaucoma in African-American populations.

Thus far, findings of genome-wide association studies have implicated eight genetic loci that show strong associations with primary angle-closure glaucoma.[35,98] These loci suggest mechanisms of cell–cell adhesion and collagen metabolism, a type 2 diabetes-related pathway, and acetylcholine-mediated signalling are important in the primary angle-closure glaucoma disease process.

Considering the results of these genetic studies, assessment of family history of glaucoma is clinically important. Having a first-degree relative with glaucoma has been associated consistently with an increased risk for primary open-angle glaucoma and primary angle-closure glaucoma in prevalence surveys. Siblings of affected individuals have nearly an eight times increased risk of primary open-angle glaucoma and a five times increased risk of angle closure when compared with siblings of unaffected individuals. The risk for primary open-angle glaucoma might be stronger when the affected relative is a sibling rather than a parent or child.

Although several genes are associated with glaucoma, the connection between the gene mutation, the secondary change in the encoded protein, and the tertiary alteration in the function of this protein are unclear. Genetic findings, therefore, have not yet contributed greatly to elucidate the pathogenesis of glaucoma.

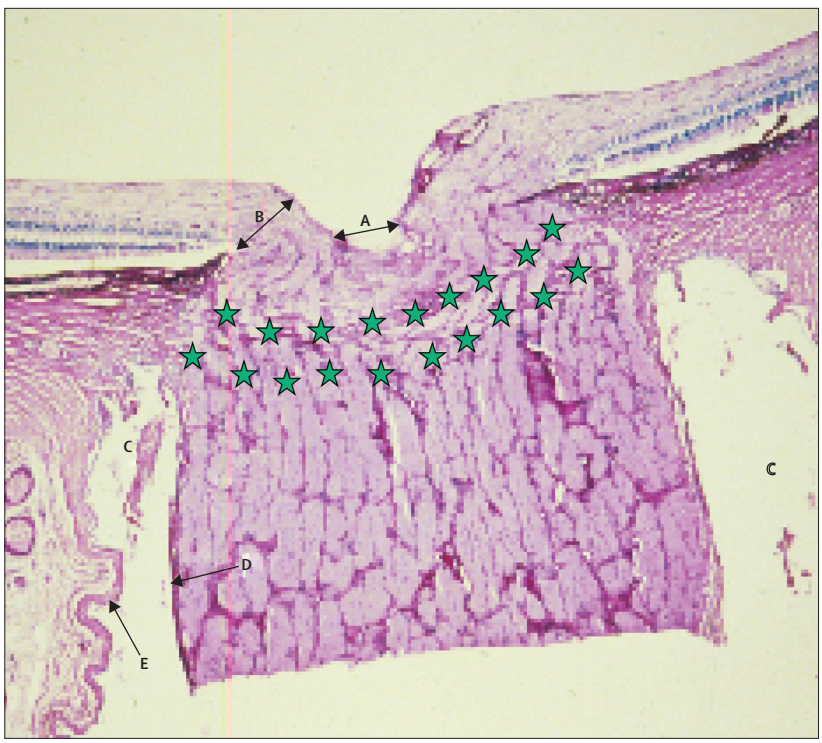

Figure 4: **Imaging of the optic nerve head**
Histophotograph shows a healthy optic nerve head with the lamina cribrosa (between the green stars) as the bottom of the optic cup (A) and the neuroretinal rim (B) containing the retinal ganglion cell axons. The orbital CSF space (C) is between the pia mater of the optic nerve (D) and the dura mater of the optic nerve (E).

Screening

A large proportion (50–90%) of patients with glaucoma remain undiagnosed in developed, developing, and underdeveloped regions of the world.[59,99] Although screening for glaucoma in the entire population would be an option, it is not considered logistically feasible. Because of the fairly low prevalence of glaucoma (about 3·5% in individuals aged 40 years or older), and since diagnostic measures with sufficient precision are not yet available, general screening for glaucoma would result in an unacceptably high number of false-positive diagnoses. Using a health economic model, Burr and colleagues[100] compared opportunistic case-finding to two proposed screening strategies for glaucoma in the UK. They found that general population screening was not cost-effective given the disease prevalence and that targeted screening of specific subgroups aligned with the established risk factors would be needed to achieve cost-effectiveness. These same reasons hold true for genetic screening for glaucoma. Therefore, for screening programmes to be effective, it is important to select participants at substantial risk. If only one screening technique could be applied, imaging of the optic nerve and retinal nerve fibre layer would currently be judged the best. One measurement of intraocular pressure has a low sensitivity to detect glaucoma under screening conditions.[101]

Diagnosis

Because chronic forms of glaucoma are painless, measurable visual-field defects do not develop at an early stage of glaucoma, and defects generally do not occur at homonymous locations in both visual fields, self-detection of glaucoma by affected individuals usually occurs at a late stage of the disease. The mainstay of detection of glaucoma is examination of the optic nerve head and retinal nerve fibre layer.[102–106] Glaucomatous changes of the optic nerve head include loss of neuroretinal rim, leading to enlargement of the optic cup, deepening of the optic cup (partly reversible if the intraocular pressure is

reduced to normal or subnormal levels), development and enlargement of the parapapillary beta zone, thinning of the retinal nerve fibre layer, and optic disc haemorrhages, which are signs of progression of the disease.[107–109] These changes can be assessed by simple ophthalmoscopy or by imaging techniques such as spectral-domain optical coherence tomography, which is useful in particular for follow-up examinations.[106,110]

Tonometry is an essential part of the diagnosis and follow-up of glaucoma, although intraocular pressure cannot be taken as the main criterion for diagnosis of the disease because many patients with glaucoma can present with normal intraocular pressure. In the Japanese population-based Tajimi study,[111] intraocular pressure was 21 mm Hg or less in 92% of patients with primary open-angle glaucoma. Intraocular pressure is the primary modifiable risk factor and its modulation is central to the management of glaucoma, but it is a fairly weak diagnostic criterion. The dependence of tonometric measurements on the central corneal thickness and curvature has to be taken into account.[112] In eyes with abnormally thick corneas, tonometry gives falsely high readings, potentially leading to overdiagnosis, and in eyes with abnormally thin corneas, tonometric measurements are falsely low, with the risk of underdiagnosis of glaucoma. Central corneal thickness and corneal curvature should, therefore, be measured once so that tonometric readings can be corrected accordingly.

Perimetric visual-field examination is the second technique in the diagnosis and follow-up of glaucomatous optic-nerve damage.[7,47,48] Many optic nerve fibres can be lost before perimetric defects are detected; therefore, the diagnostic precision of this technique increases with the stage of glaucoma.[113] Perimetry describes the subjective psychophysical defect as experienced by the patient, but it has fairly high intervisit variability, so at least three perimetric examinations could be necessary to detect visual-field deterioration reliably. Other psychophysical tests—including assessment of glaucoma-related colour vision deficiency, impaired dark adaptation, increased photophobia, and decreased contrast sensitivity—are important for the quality of vision of the patient. These modalities, however, are not measured routinely because of high interindividual and intraindividual variability.

A potential future development is application of optical coherence tomography angiography to visualise the superficial and deep retinal vascular network and, in particular, the peripapillary radial vascular network.[114] Assessment of the peripapillary radial vascular network could help in the diagnosis and follow-up of glaucomatous optic neuropathy in highly myopic eyes, in which most other diagnostic methods fail.

Open-angle glaucoma is distinguished from angle-closure glaucoma by gonioscopic examination of the anterior chamber angle. Angle-closure glaucoma in its chronic form can be asymptomatic until visual-field defects are noticed. In its acute form, angle-closure glaucoma is caused by an acute pupillary block and is characterised by an inflamed eye with pronounced hyperaemia of the conjunctiva, corneal oedema, a mid-dilated unreactive pupil, a shallow anterior chamber, and high intraocular pressure. Acute angle-closure glaucoma is usually accompanied by severe ocular pain with blurring of vision, haloes noticed around lights, nausea, and vomiting.

Treatment

Open-angle glaucoma

The only proven and generally accepted treatment to reduce the risk of further progression of glaucomatous optic neuropathy is to lower intraocular pressure.[49,51,115] Reduction of intraocular pressure is achieved by drug treatment, laser therapy, or surgery. The goal is to lower the intraocular pressure towards an individual target level at which further progression of glaucomatous optic nerve damage is unlikely. The target intraocular pressure for a particular eye is estimated based on the pretreatment intraocular pressure, the severity of damage, presence of risk factors for progression, life expectancy, and potential for adverse effects from treatment. The aim is usually for a reduction in intraocular pressure of 20–50%. The greater the pre-existing optic-nerve damage and the more risk factors present, the lower the target pressure is set. The target intraocular pressure should be reanalysed periodically by assessing whether the optic-nerve damage is stable or has progressed.

Several categories of topical drugs for lowering intraocular pressure are available. The choice of drug is affected by cost, adverse effects, and dosing schedules. In general, prostaglandin analogues (eg, latanoprost, tafluprost) are the first-line medical treatment; when delivered once in the evening, these drugs lower intraocular pressure by improving uveoscleral outflow. Local side-effects include elongation and darkening of eyelashes, loss of orbital fat (prostaglandin-associated periorbitopathy) with resulting enophthalmos, iris darkening in eyes with greenish-brown iris colour, and periocular skin pigmentation.

An alternative to prostaglandins are β adrenergic blockers (eg, timolol, betaxolol), which reduce intraocular pressure by decreasing aqueous humour production. Applied once (in the morning) or twice (morning and evening) daily, they can result in systemic side-effects including bradycardia, arrhythmias, a drop in blood pressure, reduced libido, and increased obstructive bronchial problems that can lead to an asthmatic attack.

Other groups of drugs include topical carbonic anhydrase inhibitors (eg, dorzolamide, brinzolamide), which reduce aqueous humour production, and α adrenergic agonists (eg, brimonidine), which decrease aqueous humour production and increase uveoscleral outflow. Miotics (eg, pilocarpine) have the longest history of application and reduce intraocular pressure by improving the transtrabecular outflow. Local side-effects are a varying

degree of annoying involuntary accommodation in patients younger than 45 years and pupillary constriction, which is inconvenient at night and can reduce visual acuity in eyes with cataract, yet increases the depth of focus because of the stenopeic effect. Miotics can, therefore, be useful in eyes with artificial intraocular lenses after cataract surgery. Miotics do not have major systemic side-effects.

Prostaglandin analogues, carbonic anhydrase inhibitors, and miotics reduce intraocular pressure during both day and night, whereas β adrenergic blockers and α adrenergic agonists are effective mostly during daytime. Most drug groups can be combined with each other.

A new class of topically applied drugs is the ρ kinase inhibitors (eg, ripasudil), which have finished phase 3 trials and are expected to be approved in 2017.[116–118] These drugs reduce intraocular pressure by increasing the transtrabecular outflow and, potentially, by decreasing the production of aqueous humour.

After topical application of an eye drop, gentle occlusion of the lower lacrimal duct—or just to close the eyes for a few minutes—is recommended. These measures greatly reduce the amount of drug passing through the lacrimal drainage system on to the mucosa of the oropharynx where the drugs are easily absorbed and, by avoiding breakdown by the hepatic system, can lead to systemic side-effects.

In eyes with an open anterior chamber angle, drug treatment could be augmented by, or in some cases replaced by, laser therapy (laser trabeculoplasty) to the trabecular meshwork, in particular if the target intraocular pressure is not achieved by use of drugs (particularly in poorly compliant patients). Independent of concurrent drug treatment, laser intervention can reduce the intraocular pressure by a few additional mm Hg. The good safety profile of laser trabeculoplasty is combined with fairly low efficacy.

If the intraocular pressure-lowering effect is not sufficient, incisional glaucoma surgery has to be done, usually under local anaesthetic but occasionally under topical anaesthesia. In patients with poor compliance or those intolerant to drug treatment, incisional surgery can also be done as the first step in the treatment of glaucoma. A panoply of surgical antiglaucomatous procedures has been developed in the past decade. Creating an additional outflow pathway from the eye for the aqueous humour, all surgical techniques (eg, trabeculectomy) risk reduced long-term success secondary to fibrosis around the subconjunctival exit point of the fistula. During and after surgery, antimetabolites are applied to the surgical site to decrease the fibrotic response and to keep the fistula site open. Glaucoma implant drainage devices are another surgical option and act by channelling the aqueous humour through a tube out of the eye into the subconjunctival space. These devices are similarly effective in lowering intraocular pressure to trabeculectomy.[119] Minimally invasive glaucoma surgery, compared with standard trabeculectomy, has fewer side-effects but lower efficacy.[120] Similarly, trabeculectomy versus non-penetrating surgeries (eg, deep sclerectomy, viscocanalostomy, and canaloplasty) is more effective at reducing the intraocular pressure but has a higher risk of complications.[120,121]

Primary angle-closure glaucoma

The treatment of acute angle closure differs profoundly from the therapeutic regimen for open-angle glaucoma. In acute angle closure, acutely raised intraocular pressure is lowered first by drugs, including miotics as first-line treatment (eg, pilocarpine), repeatedly instilled in short intervals, and other drugs used in chronic open-angle glaucoma (eg, timolol, latanoprost, brimonidine). The aim is to open up the angle by inducing a miosis and pulling the peripheral iris tissue out of the angle. An alternative could be immediate laser iridoplasty.[122] As definitive treatment, peripheral laser iridotomy, which forms a pathway for aqueous humour flow between the posterior chamber and anterior chamber by creating a small hole in the peripheral iris, is mandatory for all patients with primary angle-closure. This technique reduces the pressure differences between both chambers so that the peripheral iris can flatten and be retracted out of the anterior chamber angle. If done at an early stage, one procedure can result in lifelong cure. If the procedure is delayed, peripheral anterior synechiae can form, and if not released by surgical intervention within a few days to weeks, further circumferential adhesions can occur, resulting in an irreversible closure of the whole anterior chamber angle and blockage of the outflow system. Non-pupillary block mechanisms (eg, plateau iris) can cause a considerable proportion of angle closure in people from east Asia, an ethnic group that has a higher propensity for angle-closure glaucoma.

Post-iridotomy procedures to further lower intraocular pressure, if needed, are similar to those undertaken for the treatment of open-angle glaucoma. They include topical application of anti-glaucomatous drugs and incisional anti-glaucoma surgery, including trabeculectomy or lens extraction with implantation of glaucoma drainage implants. Since the risk of acute angle closure is usually similar between both eyes, laser peripheral iridotomy should be done prophylactically in the contralateral eye of a patient presenting with unilateral primary angle closure. Evidence from a clinical trial shows that clear-lens extraction has greater efficacy and is more cost-effective than laser peripheral iridotomy for treatment of primary angle-closure glaucoma,[123] and this technique could be considered as an option for first-line treatment. In more than 400 patients with either newly diagnosed primary angle closure and an intraocular pressure of 30 mm Hg or greater or primary angle-closure glaucoma,[123] individuals assigned to undergo clear-lens extraction versus standard care with laser peripheral iridotomy and topical medical treatment showed at study end a significantly higher mean health status score (p=0·005), a lower mean intraocular pressure (p=0·004), and an incremental cost-effectiveness

ratio of £14 284. The study findings agreed with those of a previous investigation,[124] in which cataract surgery combined with goniosynechiolysis successfully normalised the intraocular pressure in patients with persisting peripheral anterior synechiae between iris and cornea and raised intraocular pressure after periphery iridotomy.

Congenital glaucoma

Treatment of congenital glaucomas is mainly surgical. Procedures used include goniotomy or trabeculotomy, in which the inner wall of Schlemm's canal is opened into the anterior chamber.

Future developments

The noted growth in prevalence of cataract surgery and the increase in prevalence of axial myopia, in particular in Asia, might decrease the occurrence of angle-closure glaucoma in the future.[125] Ongoing studies that investigate the benefits of iridotomy in patients with angle closure from east Asia will provide guidance on the efficacy of this treatment in these populations, in which angle-closure is fairly prevalent among adults.[126]

Topically applied ρ kinase inhibitors might become an additional pillar in the medical treatment of glaucoma.[116–119] Novel sustained-release delivery systems—eg, intracameral injection of slow-release intraocular pressure-lowering drug pellets or topically applied cyclodextrins—are being tested in trials.[127,128] Such systems might reduce the problems associated with poor adherence and ocular surface damage that can occur with long-term use of topically applied eye drops.

Better understanding of patient-reported outcomes and experience might further improve the practical success of glaucoma treatment.[129] Furthermore, improved awareness of the many forms of glaucoma among the general population and health-care professionals, in particular among adults with a family history of glaucoma, will address the large proportion of disease that has remained undetected so far, even in high-income countries.[59,99]

Ongoing research will further refine the morphological diagnosis of glaucoma, in particular the measurement of the thickness of the retinal nerve fibre layer and the width of the neuroretinal rim. These data will help to improve precision in detecting progression of glaucomatous optic nerve damage.[103–106]

Ongoing studies will assess the hypothesis that in patients with primary open-angle glaucoma and normal intraocular pressure, the orbital CSF pressure could be abnormally low, so that the translamina cribrosa pressure difference would be raised.[21,22,67,68] These studies might also examine dynamic changes of the optic nerve head that occur with non-simulataneous changes in intraocular pressure and CSF pressure.

Several areas for future research are possible. First, studies are needed to investigate secondary involvement of the retinal microglial cells in the process of retinal ganglion cell damage.[130] Second, work is awaited to elucidate secondary intracranial changes, including cerebral neuroplasticity.[37] Third, research is needed to examine the role of retinal vein pulsations and retinal venous blood pressure in the pathogenesis and diagnosis of glaucomatous optic neuropathy.[131] Fourth, an assessment should be done of the cause of parapapillary beta zone.[132] Fifth, investigations are needed into the reasons for increased glaucoma susceptibility in patients with high myopia.[53–56] Finally, research is awaited into the biomechanics of the optic nerve dura mater and its effect on the optic nerve head.[57]

Another area for future development is to further investigate exfoliation syndrome, with respect to its genetics, proteomics, molecular biology, cellular processes, and systemic manifestations.[133,134]

Several potential novel treatments for glaucoma are under investigation or could be explored. First, studies are underway to investigate induction of a re-sprouting of retinal ganglion cell dendrites to increase the receptive field of the still-existing ganglion cells.[135] Second, studies are in progress to refine the existing surgical techniques to reduce the risk of a postoperative scarring of the filtering bleb, leading to treatment failure. Finally, work to further assess the application of stem cells and gene therapy in patients with glaucoma is needed.

Contributors

JBJ, TA, RRB, AMB, RR, and SP-J jointly searched the literature and prepared and revised the manuscript and approved it.

Declaration of interests

JBJ is a consultant for Mundipharma; holds a patent with Biocompatibles UK (patent number 20120263794); and has applied for a patent with the University of Heidelberg (Europäische Patentanmeldung 15 000 771.4). TA is a consultant for Alcon, Allergan, Belkin Lasers, Carl Zeiss Meditec, Pfizer, Roche, Quark, and Santen; has received lecture fees, travel grants, and research support from Alcon, Allergan, Roche, Santen, and Tomey; has received lecture fees and research support from Carl Zeiss Meditec; and has received research support from Ellex, Ocular Therapeutics, and Quark. RRB is a consultant for and has received lecture fees, travel grants, and research support from Allergan and Tomey; and is a consultant for and has received lecture fees and travel grants from Santen. AMB is a consultant for Allergan, Bausch-Lomb, and Théa; and has received research support from Théa and Horus. RR has received personal fees from Sensimed AG, iSonic Medical, Aeon Astron Europe, Santen Pharmaceutical, Ocular Instruments, Gerson Lehrman Group, Gillis Zago Professional, Donahey Defossez & Beausay, Tanoury, Nauts, McKinney & Garbarino, Diopsys, GLIA, Guardion Health Sciences, Mobius Therapeutics, Intelon Optics, Xoma, and The International Eye Wellness Institute. SP-J holds a patent with Biocompatible UK (patent number 20120263794) and has applied for a patent with the University of Heidelberg (Europäische Patentanmeldung 15 000 771.4).

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