The glaucomas

Glaucoma is the second commonest cause of blindness worldwide, after cataract. Recent developments include new topical antihypertensive drugs and anti-scarring drugs in glaucoma surgery. Improved techniques for imaging the optic nerve are enabling early diagnosis and identifying progression of disease.

Glaucomatous optic neuropathy is the leading cause of irreversible blindness, affecting around 70 million individuals with at least 6.8 million bilaterally blind (Quigley, 1996). The glaucomas as a group have in common a progressive degeneration of retinal ganglion cells and their axons, resulting in a distinct appearance of the optic disc and a concomitant pattern of visual loss (Weinreb and Khaw, 2004). More than 7 million outpatient visits per year are required to monitor glaucoma in the USA.

In understanding the glaucomas, a distinction is made between those conditions in which the corneoscleral drainage angle is open and those in which changes in the anatomical structure of the angle have led to a decreased outflow facility in the eye (*Figure 1*).

However, even with an open angle, outflow may be impeded by a trabecular meshwork rendered dysfunctional by the presence of particulate matter such as cellular debris, leading to a rise in intraocular pressure (IOP) and pathological changes. These, along with other conditions, are regarded as secondary glaucomas. In congenital glaucoma, the trabecular meshwork and associated structures may fail to develop normally.

The presentation of the glaucoma will depend on the causative mechanism. This ranges from asymptomatic mild peripheral visual field loss in open angle glaucoma to an acute painful blind red eye associated with very high IOP in angle closure glaucoma. Sadly, late presentation of asymptomatic open angle glaucoma with advanced field loss is a regular occurrence, even in developed countries.

Neuronal death is not limited to changes in the retinal ganglion cell axons, soma and dendrites; neurons in the lateral geniculate nucleus and the visual cortex also degenerate.

The goal of glaucoma treatment as suggested by the European Glaucoma Society (2003) can be summarized as follows: preservation of visual function adequate to the individual needs with minimal or no side effects, for the expected lifetime of the patient, with minimal disruption of his/her normal activities at a sustainable cost.

Mr Jonathan Clarke *is Specialist Registrar in Ophthalmology and Research Fellow at Ocular Repair and Regeneration Biology Unit, Institute of Ophthalmology, London EC1V 9EL,* **Mr Gerry Clare** *is Specialist Registrar in Ophthalmology, Hillingdon Hospital, Uxbridge and* **Professor Peng Tee Khaw** *is Consultant Ophthalmic Surgeon, Moorfields Eye Hospital, London, and Professor of Ocular Repair and Regeneration Biology, Institute of Ophthalmology, University College, London*

Correspondence to: Mr J Clarke

Open angle glaucoma

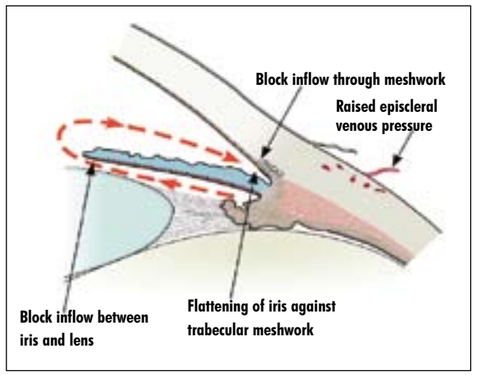
Primary open angle glaucoma (POAG) is the commonest form of glaucoma in European and African populations (Weinreb and Khaw, 2004). Gonioscopic examination reveals an open iridocorneal angle with no observed abnormalities, but the resistance to aqueous outflow occurs because of microscopic changes in the drainage system. The level of IOP is the major risk factor for the progressive loss of visual field typically found in glaucoma. It is usually bilateral and asymmetrical. In a minority of patients, POAG can advance aggressively at a young age, whereas a more typical presentation is in the fifth to seventh decades. A family history of POAG increases one's risk of developing the disease up to eightfold compared to the general population (Tielsch et al, 1994).

Diagnosis of POAG

Characteristic changes in the optic disc may be identified on direct ophthalmoscopy or slit-lamp biomicroscopy (*Figure 2*).

A formal automated visual field can effectively document visual field loss corresponding to visual pathway neuronal loss (*Figure 3*). Some estimates suggest that nearly 50% of axons need to be lost before automated visual field analysis detects an abnormality. Newer techniques have been developed that seek to identify loss of retinal cells damaged preferentially in the early stages of POAG, such as short wave automated perimetry.

Figure 1. Diagram showing normal flow of aqueous through the eye and mechanisms by which this may be disrupted.



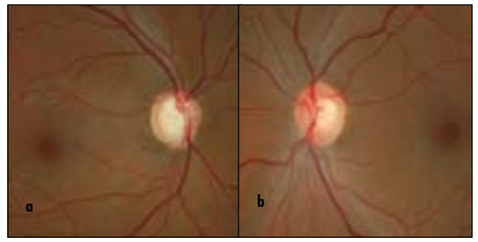


Figure 2. Optic discs of the same patient. The right (a) demonstrates pathological cupping. The left nerve (b) has a normal cup to disc ratio.

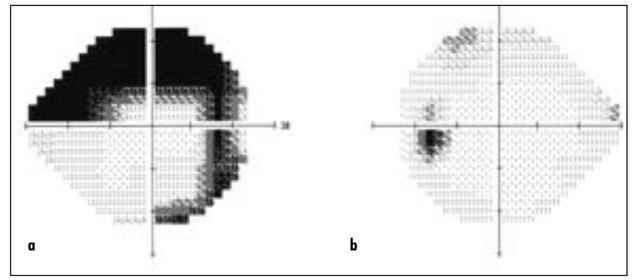


Figure 3. Automated visual fields for the same patient as in* Figure 2*, demonstrating (a) extensive loss of the peripheral vision of the right eye and (b) a maintained field of vision for the left eye.

Optic disc changes may be subtle, particularly if associated with other disc abnormalities such as in myopia. Other less common causes of optic neuropathy, such as compressive pituitary lesions, may mimic glaucomatous discs.

IOP is frequently measured by a technique known as Goldmann applanation tonometry (*Figure 4*).

Most patients are asymptomatic. Raised IOP is detected most commonly through screening as part of a routine eye test by an optometrist. In a British Caucasian population 95% of people have an IOP between 10 and 21 mmHg. The rate at which raised IOP causes optic nerve damage depends on many factors including the level of the IOP and whether the glaucomatous damage is early or advanced. In general IOPs in the 20–30 mmHg range cause damage over several years, but high IOPs in the 40–50 mmHg range can cause rapid visual loss and precipitate retinovascular occlusion.

Management of POAG

Lowering the IOP in early glaucoma has been demonstrated to reduce the risk of visual field progression (Heijl et al, 2002). Despite all forms of treatment some POAG sufferers progress unremittingly towards eventual blindness but with early detection the likelihood of subsequent blindness is low.

A large study of the benefits of lowering IOP in individuals with ocular hypertension (without field or disc changes) found that 90% of participants in the untreated group showed no evidence of glaucoma. In the remaining 10% new field or optic disc changes were identified. In the treatment group with lower IOP the risk of developing glaucoma was reduced to 5% (Kass et al, 2002).

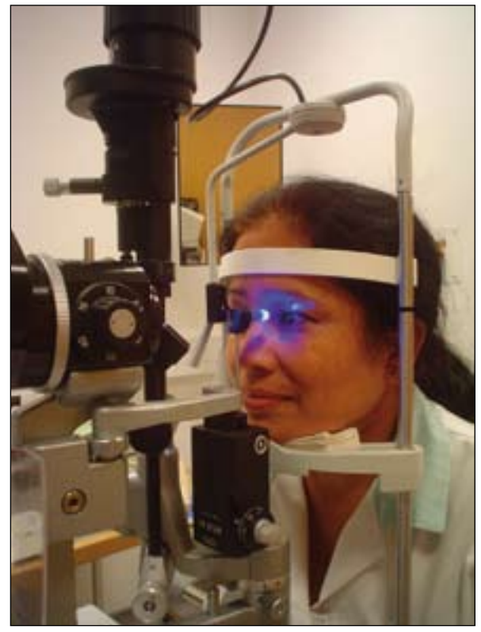
Neuronal degeneration occurs at normal IOP as part of the ageing process, and because IOP is subject to diurnal variation a single normal reading in no way excludes a diagnosis of POAG.

Measuring the true IOP depends on the biomechanical properties of the eye such as corneal thickness, scleral elasticity and shape. Corneal central thickness (CCT) may be measured in clinic by ultrasound pachymetry. Evidence suggests that reduced corneal central thickness is a risk factor for future glaucomatous progression in otherwise normal eyes with ocular hypertension (Brandt et al, 2001).

Evidence of visual field loss, or characteristic optic nerve head pathology, in association with elevated IOP is the principal requirement for a diagnosis of POAG. Visual field defects can be caused by other visual pathway pathology and visual field testing requires comprehension and cooperation on the part of the patient.

Glaucoma with normal or low IOP (normal tension glaucoma) accounts for up to 30% of open angle glaucomas. Nocturnal systemic hypotension is thought to be an important contributor, and patients on antihypertensive

Figure 4. Patient at slit-lamp undergoing applanation tonometry.



medications are at particular risk. The pathophysiological mechanism may be reduced optic nerve perfusion. Further reduction of IOP has been shown to prevent glaucomatous progression even in this group of patients who have never had a documented IOP outside of the normal range (Collaborative Normal Tension Glaucoma Study Group, 1998).

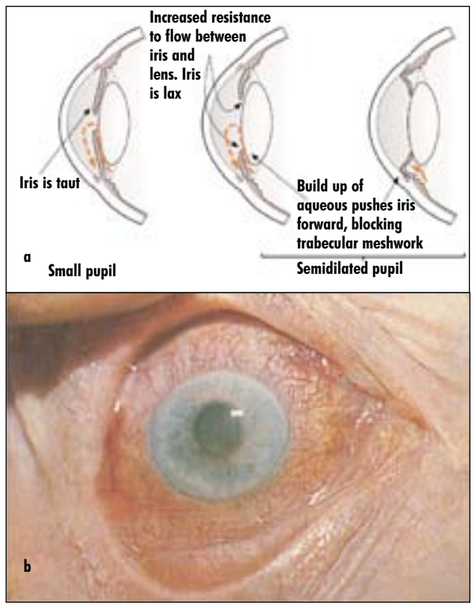
Angle-closure glaucoma

Acute angle-closure glaucoma (*Figure 5*) is a dramatic presentation and an ophthalmic emergency most commonly affecting the elderly.

IOP may rise to 70 mmHg and above, and is associated with headache, malaise and vomiting, blurred vision and a red eye. This presentation is sometimes preceded by intermittent redness, ocular pain and seeing haloes around light. Angle closure may be precipitated by iris dilatation in dark conditions. Risk factors include a small eye, as in hypermetropia, or a large cataractous lens displacing the iris–lens diaphragm forward, shallowing the anterior chamber and narrowing the angle. The large cataract impedes the passage of aqueous through the pupil and this fluid pushes the iris forward, compounding the problem. Iris–lens adhesions caused by intraocular inflammation may add to the pupil block and give rise to a characteristic finding called iris bombé in which the iris is bowed forward.

Treatment of acute angle closure may involve both topical and systemic therapy to bring about an abrupt drop in IOP. Direct pressure on the cornea may help to force the angle open and increase drainage. Once the cycle is broken, a peripheral iridotomy (by neodymium: yttrium-aluminium-garnet laser or surgical means) is usually required to equalize the pressure between posterior and anterior chambers (*Figure 6*).

Figure 5. a. Diagram showing mechanism of angle closure and (b) external appearance of an eye with angle closure.



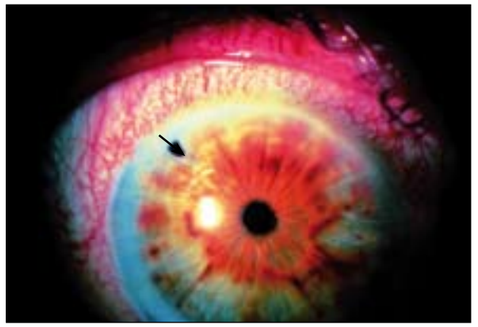


Figure 6. Patent peripheral iridotomy (arrowed) in superior iris.

This is often useful in intermittent and chronic angle-closure, although if the trabecular meshwork is severely damaged by scarring a more definitive surgical treatment may be necessary.

Secondary glaucoma

This rarer group of conditions collectively lead to progressive loss of ganglion cells usually with raised IOP. The pathophysiology of the IOP rise depends on the underlying disease.

Trabecular meshwork obstruction

Myopic individuals typically in their third decade sometimes have a particular lens–iris configuration in which frictional movement of a concave iris provokes a characteristic dispersion of pigment into the anterior chamber and drainage angle. With time, pigment dispersion syndrome may lead to a sustained increase in IOP.

Certain racial groups exhibit proteinaceous deposits on the anterior lens capsule, known as pseudoexfoliation. Like pigment, this material can obstruct the trabecular meshwork and lead to glaucoma, usually in later life. Intraocular haemorrhage may also obstruct the trabecular meshwork with a subsequent raised IOP that is usually transient. Fibrovascular proliferation within the angle may cause secondary closure in ischaemic conditions such as central retinal vein occlusion and occasionally proliferative diabetic retinopathy (*Figure 7*).

Uveitic glaucoma

A number of inflammatory ocular conditions lead to intermittent rises in IOP and may produce glaucomatous damage at any age. They include choroidoretinal toxoplasmosis, herpes simplex, ocular sarcoid and juvenile chronic arthritis (pauciarticular subtype).

Unfortunately, the topical steroid drops frequently used to treat these conditions may also cause IOP to rise dangerously in about one third of patients who are steroid responders.

Raised episcleral venous pressure

Fistulae between the arterial and venous circulations of the eye, caused by traumatic or vasculopathic mechanisms, may cause secondary rises in IOP by increasing the episcleral venous pressure. Aqueous drains from the trabecular meshwork down a pressure gradient into these vessels. Raised episcleral venous pressure is the mechanism for the development of glaucoma associated with Sturge–Weber syndrome.

Epidemiology of glaucoma

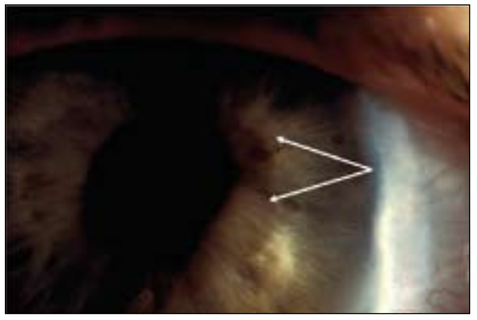
Racial differences in the type and age of presentation of glaucoma have been well documented. In surveys of European-derived populations the rates of blindness in patients with glaucoma were estimated at 4.4% while in African Americans the estimate was 7.9% (Tielsch et al, 1991). In addition blindness presents at a younger age in the African Americans and the burden of disease is far greater in this population. The prevalence of POAG is common in Europeans compared to the other forms of glaucoma (90%) but angle-closure glaucoma accounts for 50–75% of glaucoma cases in East Asian population (Husain et al, 2005). This is a result of the anatomical differences of the iridocorneal angle.

In regions where consanguineous marriage is commonplace, such as the Middle East, higher rates of congenital glaucoma are found.

Imaging

Modern imaging techniques aim to quantify glaucomatous change. A combination of imaging methods significantly increases the capability to distinguish normal eyes from those with early to moderate glaucoma (Greaney et al, 2002). These include stereo photographs of the optic nerve head, confocal scanning laser ophthalmoscopy and optical coherence tomography (OCT).

Figure 7. New vessels at the iris.



Stereo photographs can provide a record for later comparison. This is achieved by fundus cameras which take two pictures of the disc at a different angle to each other and which can then be viewed stereoscopically to give the impression of depth.

Heidelberg retinal tomography uses confocal scanning laser imaging to measure numerous features of the optic disc, including cup:disc ratio (*Figure 8*).

OCT is a method of visualizing fine cross-sections of the retina and can measure nerve fibre layer thickness and optic nerve head parameters to help diagnose glaucoma (Medeiros et al, 2004). OCT uses infrared light in a similar way as B scan ultrasound, but achieves a resolution which is an order of magnitude higher than ultrasound.

Multifocal electroretinograms measure electrical transmission at specified locations of the retina and along particular neural pathways associated with glaucoma, but their routine use in glaucoma imaging is not yet established.

Medical treatment

Eye drops have advantages over systemic medications in the treatment of chronically raised IOP in that they are delivered directly to the target organ and thus have fewer systemic side-effects. Oral and intravenous antiglaucoma therapies are effective in the management of acute glaucomas or very high rises in IOP, when decompressing the eye is necessary for its survival.

Five different classes of eye drops are in use to treat glaucoma in modern practices (*Table 1*). They are: beta-blockers, alpha-2-agonists, carbonic anhydrase inhibitors, miotics (cholinergic agents), and the most recent

Figure 8. Confocal scanning laser image showing optic disc changes and abnormal sectors of the nerve head.

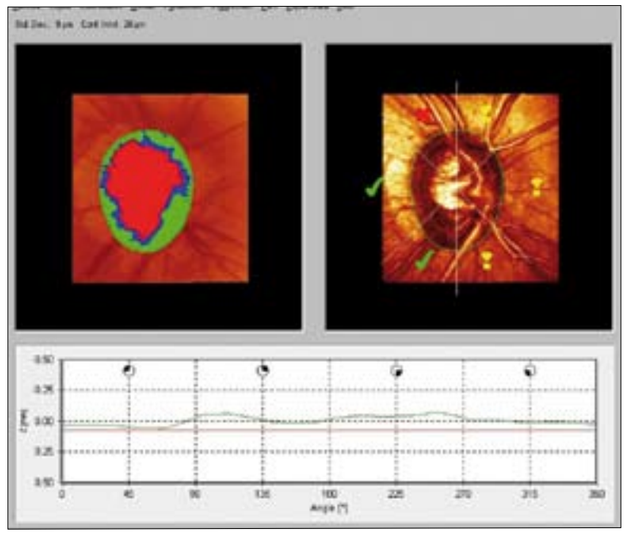


Table 1. Agents that reduce intraocular pressure

		Examples	Side-effect
Agents that suppress aqueous inflow	Beta-adrenergic blockers	Betaxolol, carteolol, timolol, levobunolol, metipranolol	Ocular irritation and dry eyes. Contraindicated in patients with heart block, bradycardia, heart failure, asthma or obstructive airway disease
	Alpha-adrenergic agonists	Apraclonidine, brimonidine	Red eye and ocular irritation. Caution in patients with cerebral or coronary insufficiency, Raynaud's, postural hypotension, hepatic or renal impairment
	Carbonic anhydrase inhibitors	Dorzolamide and brinzolamide (topical), acetazolamide and methazolamide (oral)	Oral form can cause transient myopia, nausea, diarrhoea, loss of appetite and taste, paraesthesiae, lassitude, renal stones, and haematological problems. Topical forms much less likely to cause systemic side-effects but can cause local irritation and redness
Agents that increase aqueous inflow	Prostaglandin analogues (prostamide)	Latanoprost, travoprost, unoprostone (bimatoprost)	Brown discolouration of iris, lengthening and darkening of eyelashes, ocular irritation and redness, macular oedema or iritis in susceptible individuals
	Cholinergic agonists (miotics)	Pilocarpine, carbachol	Ciliary spasm leading to headaches especially in younger patients, myopia, dim vision (small pupil). Cataracts and iris–lens adhesions in long term

addition, prostaglandin analogues. They work by reducing aqueous production by the ciliary body, increasing outflow from the trabecular meshwork and the uveoscleral pathways, and, in the case of miotics, by altering the anatomical structure of the angle to prevent closure. Tachyphylaxis, or a long-term drift in efficacy, is a problem affecting beta-blockers in particular. Patients may be intolerant to eye drops or the preservatives used to prolong their shelf-life. Local side-effects include ocular allergy and irritation (*Figure 9*).

Preservative-free unit doses, available for some medications, are prescribed when the ocular surface is susceptible to damage or when polypharmacy cannot be avoided. Eye drops can cause systemic side-effects, and beta-blockers in particular are sometimes avoided or suspended because they can exacerbate breathlessness or bradycardia.

Surgical treatment

Surgery may result in a lowering of IOP that is superior to medical treatment, but surgical complications and increased rates of cataract formation may mitigate the effects on vision (Lichter et al, 2001). A variety of surgical treatments are available, including filtration procedures, drainage implants, laser to the trabecular meshwork and ablation of the ciliary body. The choice of procedure depends on a number of factors including patient factors, disease factors and surgical preference. Choosing the right procedure is of paramount importance. The operations may be technically challenging and the postoperative care is critical to the success or failure of the procedure.

The technique in most widespread use is the trabeculectomy, whereby a fistula is created between the anterior chamber and the subconjunctival space (*Figure 10*).

The single most important cause of failure of the filtration procedures has been the tendency of the tissues to scar. The advent of anti-scarring agents such as the antimetabolites mitomycin-C and 5-fluorouracil has reduced the failure rate of these procedures. Surgeons are able to manipulate the scarring response by the judicious application of anti-scarring agents at the site of surgery either intra- or postoperatively. The scleral trap door is secured with fixed adjustable sutures and the tension of the sutures can be adjusted in the early postoperative phase (*Figure 11*).

This may have particular importance in the developing world, where medical treatment of glaucoma has inherent problems (Yorston and Khaw, 2001).

Potential sight-threatening complications include endophthalmitis and hypotony.

Figure 9. Patient showing severe local allergic reaction to topical preservatives.

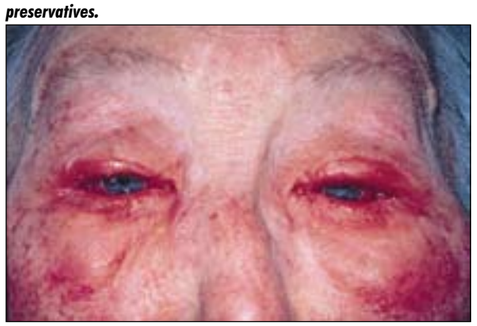
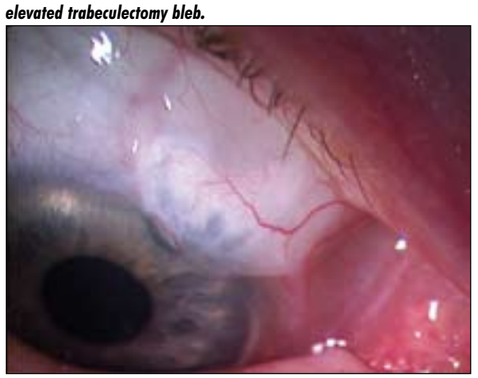


Figure 10. Photograph at slit-lamp demonstrating functional, elevated trabeculectomy bleb.



The future

Given the burden of visual loss attributable to glaucoma, it is an area where research possibilities abound, and it may one day be possible to add glaucoma to the list of preventable diseases (Frick and Foster, 2003). The great impact of the anti-mitotic agents in glaucoma surgery has led to the search for new, less toxic agents, such as growth factor inhibitors (Siriwardena et al, 2002). A need to slow neurodegeneration of the visual pathway has stimulated research into neuroprotective agents such memantine with positive results in early trials (Hare et al, 2004). The complex genetic combinations giving rise to increased risk of glaucoma are gradually being elucidated. Imaging techniques are being refined in order to identify early signs of disease before the onset of visual loss. An ever-greater understanding of the complex problem of the glaucomas is needed to identify strategies for the prevention of blindness. BJHM

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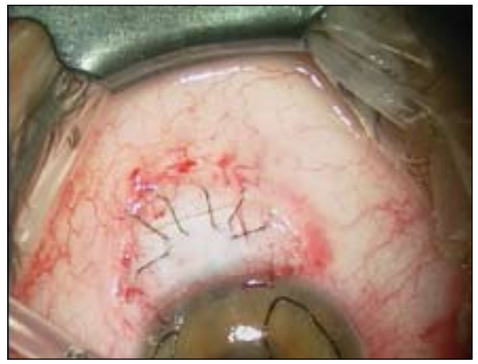
Figure 11. Six adjustable sutures placed around the scleral flap. The tension of these and subsequent flow of aqueous can be adjusted in the postoperative period.



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KEY POINTS

- The glaucomas are a heterogeneous group of diseases which all show progressive, irreversible optic nerve changes and loss of visual field.
- Visual loss from glaucoma may be prevented.
- In many patients, topical pressure-lowering therapy has obviated the need for surgery.
- Anti-scarring agents in surgery are used to reduce postoperative failure.
- Improved imaging is can help to diagnose glaucoma and to quantify its progress.