

CME

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Glaucoma

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Glaucoma is one of the most common ophthalmic conditions encountered in primary and secondary care. The World Health Organization estimated that in 2010 glaucoma accounted for 2% of visual impairment and 8% of global blindness.¹ Disability adjusted life years attributable to glaucoma more than doubled between 1990 and 2010 due to the worldwide increase in the number of older people.² Glaucoma is the leading cause of irreversible blindness in the world. In the United Kingdom, the management of patients with glaucoma constitutes a major part of ophthalmologists' workload, accounting for 23% of all follow-up attendances to the UK hospital eye service.³ In the NHS there are more than one million glaucoma related visits per year. The social and economic burden is likely to increase in the future because of longer life expectancy and an ageing population.⁴⁻⁵ In the UK, glaucoma is the second most common cause for registration of visual impairment, accounting for 9-12% of registrations in people over the age of 65 years.⁶

What is glaucoma?

Glaucoma refers to a group of conditions with heterogeneous causes that results in damage to the optic nerve head and loss of visual field. It is usually associated with an increase in intraocular pressure (IOP) above the normal value—usually estimated at 21 mm Hg (mean 15.5, ±2 standard deviations, range 10-21). However, surveys show that 20-52% of patients with glaucoma have IOP within the normal range. Primary open angle glaucoma is the most common type of glaucoma, accounting for over 70% of cases. It is an IOP related optic neuropathy that gives rise to characteristic optic disc changes and visual field loss. In its early stages it affects peripheral visual field only, but as it advances it results in loss of visual acuity and can cause blindness. Some patients with statistically normal IOP develop the characteristic changes associated with open angle glaucoma and are said to have low tension or normal pressure glaucoma.

Who gets glaucoma?

Risk factors for primary open angle glaucoma are increasing age and IOP, black ethnicity, history in a first degree relative, myopia, and diabetes (table 1).⁴⁻⁵⁻⁷

A recent meta-analysis showed a substantial variation in prevalence rates in adults according to ethnicity, with rates of 2.14 (95% confidence interval 1.72 to 2.65), 4.23 (3.07 to 5.83), and 1.41 (1.00 to 2.00) for white, black, and Asian people, respectively.⁸

A recent systematic review found an estimated prevalence of glaucoma in a mainly white population aged over 40 years of 2.1% (1.7 to 2.5).⁵ Around 67% of cases are not currently detected in Western countries. In white people, the overall prevalence of glaucoma is 0.3 (0.1 to 0.5) in people aged 40 years but increases sharply to 3.3% (2.5 to 4.0) in those aged 70 years.

Advanced glaucoma at presentation is the main risk factor for blindness. In a recent UK survey, 39% of patients with glaucoma presented with advanced disease in at least one eye.⁹ Those most at risk include socially disadvantaged people with no family history of glaucoma, those with high IOP, and those who do not attend an optometrist regularly.⁹⁻¹¹

Identifiable gene mutations are implicated but account for only about 5% of cases of adult onset glaucoma.¹² Although certain genetic subtypes are more likely to progress towards severe disease, current knowledge of the inheritance of open angle glaucoma suggests that genetic screening would not detect a substantial number of the currently undetected cases.

How is glaucoma classified?

Glaucoma is classified into two major categories according to the appearance and obstruction of the drainage pathway at the iridocorneal angle (trabecular meshwork) (fig 1). In open angle glaucoma, despite the normal clinical appearance, the aqueous outflow is restricted, and in closed angle glaucoma tissue physically obstructs the angle.

Glaucoma can also be classified according to whether it is primary (idiopathic; the most common type) or secondary—associated with detectable comorbidity. Such comorbidities include pseudoexfoliation; rubeosis associated with ocular ischaemia due to vascular occlusion or diabetes; uveitis; or after ocular surgery, such as retinal detachment surgery.

The pathophysiology of primary open angle glaucoma is not well understood. Increased IOP is common and thought to be caused by increased resistance to aqueous

SUMMARY POINTS

The treatment of glaucoma can prevent or slow visual loss
A large proportion of people with glaucoma remain undiagnosed
Patients with advanced glaucoma at diagnosis are at greatest risk of blindness
The only treatment strategy with supporting evidence is the lowering of intraocular pressure
Non-adherence to glaucoma treatment drops may contribute to disease progression

SOURCES AND SELECTION CRITERIA

This review focuses mainly on the diagnosis and current treatment options for primary open angle glaucoma, which is the most prevalent form in the United Kingdom. We searched Medline, the *Cochrane Database of Systemic Reviews*, and *Clinical Evidence* online using the search terms “glaucoma”, “glaucoma diagnosis”, “glaucoma medications”, and “glaucoma surgery”. We limited our studies to those conducted in adults and focused on systematic reviews, meta-analyses, and high quality randomised trials when available.

Table 1 | Risk factors for glaucoma⁵

Risk factor	Pooled % prevalence (95% CI)	Pooled adjusted relative risk (95% CI)
Black ethnicity	Not available	3.8 (2.6 to 5.6)
Intraocular pressure >26 mm Hg	Not available	12.6 (5.1 to 31.2)
Myopia	2.7 (1.5 to 3.9)	1.9 (1.5 to 2.3)
Diabetes	3.3 (1.8 to 4.8)	2.1 (1.4 to 3.0)
Family history	6.7 (5.0 to 8.4)	3.1 (2.3 to 4.5)

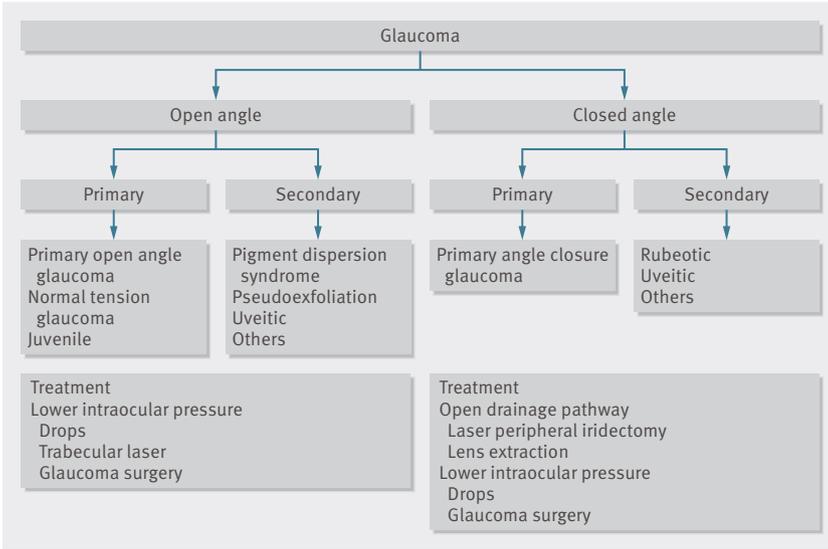


Fig 1 | Classification of glaucoma by mechanism and appearance of the anterior chamber angle. Patients with primary and secondary closed angle glaucoma can present with acute attacks. These are characterised by very high intraocular pressure and symptoms such as headache, nausea, vomiting, and blurred vision

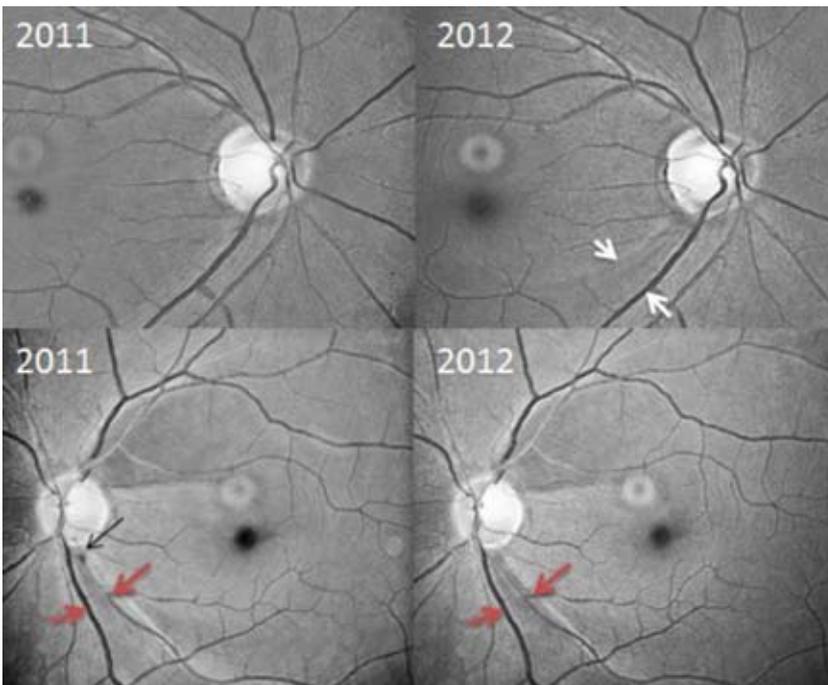


Fig 2 | The top panel shows the development (over 12 months) of a nerve fibre layer defect (darker wedge between white arrows) in a patient with early glaucoma emanating from the edge of the optic disc. The bottom panel (left eye of the same patient) shows a disc margin haemorrhage (black arrow) with associated nerve fibre layer defect (wedge between red-brown arrows), which widens over the next 12 months

outflow at the trabecular meshwork level. Loss of vision is caused by damage to and death of retinal ganglion cells. The primary site of injury in glaucoma is thought to be the optic nerve head, where the axons of the retinal ganglion cells are grouped together.

Several factors are thought to cause or contribute to ganglion cell death. Increased pressure may mechanically compress the nerve fibres at the optic nerve head and lamina cribrosa through which they pass. Poor support from the collagenous lamina cribrosa causes stasis in axoplasmic flow. Vascular factors such as perfusion and ischaemia at the optic nerve head may have a role—for example, haemorrhages at the optic nerve head are relatively common and often predict future progression of glaucoma (fig 2).

Angle closure glaucoma is caused by ocular tissues, usually the iris, mechanically obstructing the drainage pathway and preventing aqueous outflow through the trabecular network.

What is the natural course of glaucoma?

The natural course of open angle glaucoma is variable and time dependent. In many cases glaucoma is preceded by ocular hypertension—raised IOP in the absence of structural abnormalities of the optic disc or functional abnormality of the visual field. Ocular hypertension affects 3-5% of the population over 40 years of age,¹³ but only a small proportion of these people develop glaucoma.^{14 15}

When glaucoma is manifest characteristic abnormalities can be detected in the optic nerve head, retinal nerve fibre layer, and visual field (figs 2 and 3 (bmj.com)). In most patients with primary open angle glaucoma these abnormalities progress slowly, over years, and patients remain asymptomatic until late in the disease. However progression rates are variable and some types of secondary open angle glaucoma often progress more rapidly.

Treatment slows down progression, usually through the lowering of IOP.^{16 17} A systematic review reported that age, disc haemorrhages (for normal tension glaucoma), baseline visual field loss (severity of disease), baseline IOP, and exfoliation syndrome (a subtype of open angle glaucoma) were risk factors for progression.¹⁷

By the time open angle glaucoma becomes symptomatic, severe and irreversible damage has usually occurred to the visual field in one or both eyes. In cross sectional population studies in developed countries, 3-12% of patients with glaucoma are blind in one or two eyes.⁷ Some registry based and retrospective studies report higher figures—6% blind in both eyes within 15 years and 22% within 20 years.^{7 18}

How is the disease identified?

The onset of open angle glaucoma is insidious and patients may have severe disease despite good visual acuity. Patients with early glaucoma are typically unaware that they have it, and those with more advanced disease may be aware of a shadow in their vision or a reduction in visual acuity. However, because the visual fields of both eyes overlap, a normal visual field in one eye may mask the presence of a defect in the affected eye until the disease is fairly advanced. It is difficult to diagnose glaucoma without facilities to measure IOP and evaluate optic discs and visual fields. When glaucoma is suspected, especially if recognised risk factors are present

QUESTIONS FOR FUTURE RESEARCH

Should laser trabeculoplasty be used as primary treatment for mild and moderate glaucoma?
 What is the most cost effective way of monitoring and managing ocular hypertension and manifest glaucoma?
 What role do other healthcare professionals (such as optometrists and ophthalmic technicians) and technology have in improving the efficiency of monitoring of glaucoma?
 Can we monitor glaucoma in the community?
 What is the most effective and cost effective way to prevent blindness for those presenting with advanced glaucoma?

(table 1), referral to a local optometrist or hospital eye service for evaluation is necessary.

Some patients with angle closure glaucoma may experience an acute presentation with headache, ocular pain, nausea, vomiting, and blurred vision. Sometimes there are transient symptoms of blurring of vision and halos around lights, which resolve spontaneously. Patients with angle closure glaucoma are more likely to be elderly, female, and hypermetropic. More than half of all patients with glaucoma in the developed world and about 90% in developing countries are not identified.^{5 7 19} Patients are found through a process of opportunistic case detection, and the wide variation in detection rates is explained by unequal access to care facilities and large differences in the distribution and quality of services between healthcare systems. The cost effectiveness of systematic screening for glaucoma remains uncertain.^{5 20} Screening is not recommended in the UK.

Diagnostic evaluation consists of examination of the chamber angle (for example, using gonioscopy), measurement of IOP, fundus examination, and a visual field test.^{7 21} Measurement of IOP shows sizeable interobserver and intraobserver variability.²¹ Even if evaluation of IOP was reliable, alone it is insufficient for diagnosis and screening because it misses 20-52% of patients with manifest disease.²²

Accurate detection of glaucoma is challenging, particularly in early disease. In the UK a large proportion of patients referred from primary care (typically from community optometrists) for glaucoma do not have the disease. Population based studies show that 50% of newly detected patients had recently been seen by an ophthalmologist or optometrist but their disease had not been diagnosed.²⁰ Several automated technologies for imaging and measurements for visual function have been developed to aid diagnosis and follow-up of glaucoma (figs 2 and 3).

How cost effective is treatment of glaucoma and ocular hypertension?

The treatment of glaucoma has been shown to be clinically beneficial and cost effective in preventing disease progression and visual disability.^{23 24} However, it is unclear whether treating those at risk—for example, patients with ocular hypertension—is cost effective.²³

Cost effectiveness analyses of interventions typically use efficacy data based on randomised trials, which may provide optimistic estimates of outcomes compared with “real life,” where adherence to care by patients and clinicians may be poorer. More reliable and realistic data from pragmatic randomised trials or cohort studies are therefore needed.²³

What are the principles of glaucoma management?

Management aims to prevent visual disability during a patient's lifetime or, where disability exists, to prevent further deterioration.

Currently, the only modifiable risk factor is IOP, the reduction of which minimises the risk of developing glaucoma and of glaucoma progression. A meta-analysis recently assessed the effectiveness of IOP lowering treatment to delay the development of glaucoma in ocular hypertension, as well as progression of disease in those with open angle glaucoma.²⁴ It showed that lowering IOP significantly reduced progression to glaucoma (hazard ratio 0.56, 0.39 to 0.81; P=0.01;

number needed to treat (NNT) 12). Pooled data of studies in glaucoma showed a significant delay of visual field deterioration (0.65, 0.49 to 0.87; P=0.003; NNT=7), with subgroup analysis showing a larger effect in patients with raised IOP.

Once a patient is diagnosed with glaucoma a target pressure for treatment is established. This is an estimate of the IOP believed to be sufficient to prevent disease progressing to a level that would impair the quality of life. In general, the younger the patient and the more severe the glaucoma the lower the target IOP will be set.^{7 13 25} There is no universally accepted process for setting target pressure and several different approaches have been suggested.

Some patients, particularly older ones with non-severe normal pressure glaucoma, may be monitored and not treated because progression is often slow and may not result in noticeable disability during their lifetime.

For angle closure glaucoma, in addition to lowering IOP, the drainage pathway needs to be opened. A laser peripheral iridectomy, which punches a hole in the iris, or cataract surgery, which allows the iris to move away from the drainage pathway, is often successful

What are the treatment options for reducing IOP?

Medical, laser, and surgical options are available for lowering IOP. Typically, the patient is started on glaucoma drop monotherapy, with extra drops being added as required, so that two or more different types of drug can be used in cases that are difficult to control. If the maximum tolerated treatment regimen is unsuccessful, a laser intervention may be advised or the patient may proceed directly to surgery. The National Institute for Health and Care Excellence and other advisory bodies have developed guidelines to inform treatment pathways for glaucoma.^{7 13 25}

A recent Cochrane review of primary medical, laser, and surgical interventions for glaucoma suggested that a greater reduction in IOP is achieved with primary surgery than with drugs, but that surgery is associated with more eye discomfort and an increased requirement for cataract surgery in the short term.²⁶ However, the review did not include recent trials that evaluated currently available drugs for glaucoma or modern surgical methods.

Medical management

Several classes of drops are available (table 2). They lower IOP by reducing the production or increasing the outflow of aqueous humour from the eye. Prostaglandin analogues

FUTURE RESEARCH

Evaluation of technologies for diagnosing and monitoring glaucoma
 Evaluation of new drug delivery systems to ensure 24 hour control of intraocular pressure and minimise the risks of poor control associated with non-adherence
 Development of safer and more effective surgical techniques
 Evaluations of the most cost effective models of care for treating and monitoring ocular hypertension and primary open angle glaucoma
 Evaluation of the most cost effective interventions for those presenting with advanced glaucoma
 The role of neuroprotection and neuroregeneration in the treatment of glaucoma

Table 2 | Eye drops for treating glaucoma: class and mechanism of action

Class	Mechanism	Daily doses	Drug
Prostaglandin analogues	Increase outflow	1	Latanoprost*† Travoprost Bimatoprost* Tafluprost*
β blockers	Decrease aqueous production	1 or 2	Timolol*† Betaxolol*† Levobunolol* Carteolol
α agonists	Increase outflow; decrease aqueous production	2 or 3	Apraclonidine* Brimonidine†
Carbonic anhydrase inhibitors	Decrease aqueous production	2 or 3	Dorzolamide*† Brinzolamide†
Parasympathomimetic	Increases outflow	4	Pilocarpine*†

*Preservative-free preparations available; †generic preparations available.

ADDITIONAL EDUCATIONAL RESOURCES

Resources for healthcare professionals

Royal College of Ophthalmologist (www.rcophth.ac.uk/page.asp?section=484§ionTitle=Current+Issues+in+Glaucoma)—Current issues in glaucoma

The following four websites provide information about the symptoms, diagnosis, and treatment of glaucoma

European Glaucoma Society (<http://www.eugs.org/eng/default.asp>)

American Academy of Ophthalmology (<http://one.aaopt.org/ce/default.aspx>)

World Glaucoma Association (<http://www.worldglaucoma.org/>)

College of Optometrists (www.college-optometrists.org)

Resources for patients

International Glaucoma Association (www.glaucoma-association.com/)—Comprehensive source of up-to-date news and information about glaucoma

Royal College of Ophthalmologists (www.rcophth.ac.uk/page.asp?section=365§ionTitle=Information+Booklets)—Information booklets

American Academy of Ophthalmology (www.geteyesmart.org/eyesmart/diseases/glaucoma.cfm)—Information about the causes, symptoms, diagnosis and treatment of glaucoma

European Glaucoma Society (<http://www.eugs.org/eng-paz/default.asp>)—Information on ocular pressure and glaucoma

College of Optometrists (www.college-optometrists.org/en/knowledge-centre/publication/patient-leaflets/index.cfm)—Patient leaflets on glaucoma

are usually the initial treatment choice because they have the greatest IOP lowering efficacy and lowest side effect profile. If monotherapy is insufficient to control IOP additional drops are added. Many drops come as combinations of a β blocker and another drug. These combinations reduce the numbers of bottles that a patient requires and also reduce the preservative load delivered to the eye, thus reducing the risk of intolerance or allergy to the preservative used and improving adherence and persistence. Eye drops often cause transient stinging and blurring on instillation and some may cause redness, discomfort, eyelash growth, periorbital skin pigmentation, and an unpleasant taste. Systemic side effects are rare, although β blockers should be avoided in those with obstructive airways disease or heart failure.

All classes of glaucoma drops are now available as generic preparations. A variety of guidelines provide algorithms for medical treatment.¹³ Intolerance to drops (such as chronic discomfort, redness of the eye or of the skin around the eye) may be related to the preservative used. In such cases, preservative-free drugs may be used. Treatment with oral

carbonic anhydrase inhibitors (which reduce aqueous production) is usually poorly tolerated—patients may experience tingling in their fingers and toes, lethargy, and loss of appetite—making it unsuitable for long term treatment but useful for controlling acute increases in pressure or managing raised IOP in the short term while awaiting surgery.

Adherence to glaucoma drops is variable and difficult to evaluate.²⁷ It is therefore hard to know whether poor control of IOP is due to the lack of therapeutic effect or failure of patients to use the drops. Estimates of non-adherence vary greatly because there is no objective method of assessment, making evaluation of true non-adherence difficult.²⁸ Cognitive problems related to understanding the need for drops or forgetfulness, difficulty administering the drops, poor communication between doctor and patient, and a lack of engagement by the patient may contribute to poor adherence. The authors of a recent Cochrane review of interventions for adherence could not recommend any particular interventions for improving adherence.²⁹

If IOP is not controlled once the maximum tolerated treatment regimen is reached (all the drops that a patient can tolerate and acetazolamide in those who can tolerate it), laser or surgical intervention may be needed.

Laser treatment

Laser trabeculoplasty for open angle glaucoma lowers the IOP by increasing outflow and can be considered as an initial treatment option. This is a clinic based procedure. There are several laser types. Although laser trabeculoplasty is safe and effective in lowering IOP, it is not commonly used in the UK. A recent systematic review of laser trabeculoplasty highlighted the lack of data comparing the effectiveness of this procedure with modern medical and surgical options.³⁰ Cyclodiode and endocyclodiode laser of the ciliary body are used for severe glaucoma if standard surgery is not effective.

Surgery

Surgery is usually undertaken once medical or laser options for treatment have failed. However, it may be used earlier—for example, in patients with a disability that prevents them from instilling drops successfully, those in whom adherence is poor, those presenting with advanced glaucoma,¹³ and in undeveloped countries where medical management is not feasible.

The standard glaucoma operation (trabeculectomy) creates a guarded fistula into the wall of the eye (sclera), which allows a slow egression of aqueous humour from the anterior chamber into the subconjunctival space. It is often augmented with an antimetabolite agent to minimise the risk of postoperative scarring, which causes the operation to fail. This operation is successful in most patients,³¹ with about 90% of patients having an IOP of less than 21 mm Hg at 12 months. Failure of surgery will necessitate re-introduction of drops to control IOP. It is not uncommon for patients who have not already had a cataract operation to develop cataract and require cataract surgery. Severe sight threatening complications, although rare, may also occur. More recently “non-penetrating” glaucoma surgery has become popular in some countries—it does not achieve the IOP reduction of trabeculectomy but has a

lower adverse event profile. However, no large randomised controlled trials have compared these two interventions.

In cases where standard surgery is unsuccessful or for a few specific types of glaucoma, glaucoma drainage devices or “tubes” are inserted into the eye; these drain the aqueous humour from the anterior chamber into the subconjunctival space.³²

How is glaucoma monitored?

Once diagnosed, glaucoma requires lifelong monitoring, typically in secondary care. IOP is monitored and functional visual change is evaluated through visual field testing. Monitoring structural changes in the optic disc and nerve fibre layer morphology through photography, scanning laser technologies, or optical coherence tomography may also provide information on the stability or progression of the disease (figs 2 and 3). The monitoring interval depends on the severity of glaucoma and the patient's age. Typically, stable glaucoma will be monitored every six to 12 months, with advanced glaucoma or progressive glaucoma being monitored every two to four months until stable. It can be difficult to detect small amounts of visual field progression, however, because of the inherent variability in visual field testing, and several visits may be needed to establish progression.

Are there any restrictions to driving with glaucoma?

Glaucoma can impair driving ability,^{33 34} and patients may have an increased risk of motor vehicle crashes.^{35 36} Retention of driving ability is highly important to these

patients.³⁷ In the UK, visual field and visual acuity criteria are used to define eligibility to drive. Although most patients are able to drive, patients diagnosed with glaucoma are obliged to report the diagnosis to the Driver and Vehicle Licensing Agency. Severe loss of binocular visual field may affect eligibility to drive.

What future treatments are on the horizon?

Improvement in drug delivery systems to allow sustained slow release of drugs as drops or through an intraocular implant may improve adherence, improve the efficacy of these drugs to reduce IOP, and reduce ocular surface symptoms associated with the use of glaucoma drops.

Development of a therapeutic intervention that provides neuroprotection for the retinal ganglion cells that undergo apoptosis may help prevent further visual loss. To date, no drugs have shown clinical evidence of a neuroprotective effect in glaucoma.³⁸

Stem cells and gene transfer could potentially improve trabecular meshwork outflow and reduce the IOP. There is also interest in investigating the potential role of stem cell transplantation for retinal ganglion cell regeneration.

Thanks to Antti Pollari, Tays Eye Centre, for the retinal nerve fibre layer images featured in fig 1.

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References are in the version on bmj.com.

ANSWERS TO ENDGAMES, p 38

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ANATOMY QUIZ 1 Axial contrast enhanced computed tomogram of the thorax

- A: Aberrant right subclavian artery (a normal variant) arising from a left sided aortic arch
- B: Trachea
- C: Brachiocephalic artery
- D: Left common carotid artery
- E: Left subclavian artery

ANATOMY QUIZ 2 Coronal T2 weighted magnetic resonance imaging of the hip

- A: Acetabulum
- B: Gluteus minimus
- C: Greater trochanter
- D: Acetabular labrum
- E: Femoral head
- F: Femoral neck

STATISTICAL QUESTION

What is intention to treat analysis?

Statements *a*, *b*, *c*, and *d* all describe intention to treat analysis.

PICTURE QUIZ

A young woman presenting with severe headache

- 1 The image shows an area of restricted diffusion—that is, an acute infarct in the left thalamus (fig 2).
- 2 Ischaemic stroke (coexisting with migraine); migrainous infarction; embolic stroke secondary to patent foramen ovale that enables right to left intracardiac shunting; arterial dissection; vasculitis and collagen vascular diseases; cerebral vasoconstriction syndrome (including drug induced vasoconstriction); and homocysteinuria.
- 3 Clinical assessment, together with blood tests and imaging of the brain and heart to look for other causes of stroke. Thrombolysis, antiplatelet drugs, and acute supportive management should be considered.
- 4 Antiplatelet drugs and anticoagulants are established in secondary prevention of stroke. Closure of patent foramen ovale may be appropriate in selected cases.

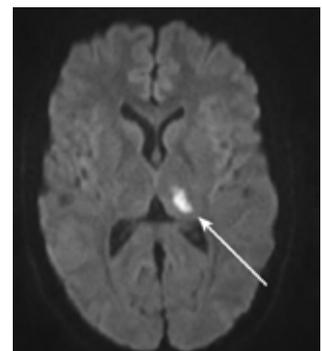


Fig 2 | Diffusion weighted magnetic resonance image of the head showing an area of increased signal (arrow) indicative of restricted diffusion that is in keeping with an acute infarct