

An Introduction to the Basic Sciences of Primary Open Angle Glaucoma



EPIDEMIOLOGY

- In the world, glaucoma is the third leading cause of blindness- an estimated 13.5 million people may have glaucoma and 5.2 million of those may be blind.

Diagnosis and Management of Primary Open Angle Glaucoma

- Glaucoma can be considered a generic name for a group of diseases causing optic neuropathy (disc cupping) and visual field loss usually , but not always, in the presence of raised IOP, it is increasingly being realised that other factors- such as optic nerve head perfusion, are concomitantly responsible for optic neuropathy in adult glaucoma.

Diagnosis and Management of Primary Open Angle Glaucoma

- **Diagnosis of Glaucoma**
- The diagnosis of glaucoma is based upon;
 - *1. Intraocular pressure (IOP) and its measurement. (tonometry)*
 - *2. Optic disc examination.*
 - *3 Visual Field examination (perimetry)*

PREVALENCE AND INCIDENCE OF POAG

- Population-based studies show that the prevalence of POAG ranges from 0.4% to 8.8% in those older than age of 40 (Table 1). On average, POAG is found in 1.9% of white and 0.58% of Asian populations. In black populations however, the prevalence is significantly higher at 6.7%. Although some of the difference can be attributed to epidemiologic study design and the precise definition of POAG, the significantly higher rates observed in Western African populations probably reflect a fundamental risk factor associated with race

- **Ethnicity**

- Ethnicity affects both the chance of an individual developing glaucoma and the prognosis of his or her disease. The Barbados Eye Study highlighted the public health importance of POAG in the Afro-Caribbean region and has implications for other populations. The prevalence of POAG by self-reported race was 7.0% in black, 3.3% in mixed-race, and 0.8% (1/133) in white or other participants. In black and mixed-race participants, the prevalence reached 12% at age 60 years and older and was higher in men (8.3%) than in women (5.7%), with an age-adjusted male-female ratio of 1.4. Among participants 50 years old or older, one in 11 had POAG, and prevalence increased to one in six at age 70 years or older.

PROGNOSIS

- Black race is another prognostic factor. At the initial time of diagnosis, blacks tend to be younger and have more advanced disease than whites.
- Glaucoma progression is more rapid and the rate of blindness from glaucoma is higher in blacks than whites
- It is generally believed that the differences are only partially explained by socio-economic factors or accessibility to medical care

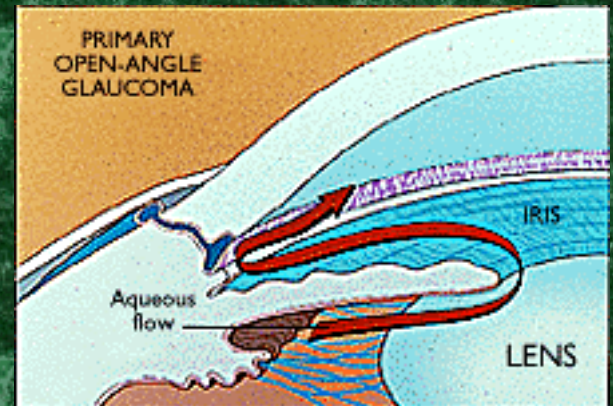
Diagnosis and Management of Primary Open Angle Glaucoma

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- Table- Estimates of the Prevalence of Glaucoma
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- Baltimore (1990) 1.3% ; 50% undiagnosed
- Ireland (1992) 1.9% ; 49% undiagnosed
- Beaver Dam (1992) 2.1%
- Rotterdam (1996) 1.1% ; 53% undiagnosed
- Blue Mountains (1996) 2.4% ; 51% undiagnosed
- Melbourne VIP (1997) 1.7% ; 50% undiagnosed
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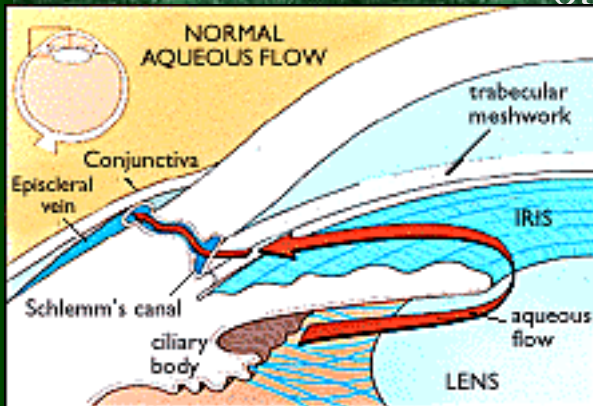
- The Blue Mountains Eye Study provided detailed age and sex-specific prevalence rates for open-angle glaucoma and ocular hypertension in an older Australian population found a prevalence of 3.0% for POAG. Ocular hypertension, defined as an intraocular pressure in either eye greater than 21 mmHg, without matching disc and field changes, was present in 3.7% of this population (95% CI, 3.1-4.3), but there was no significant age-related increase in prevalence. This correlates with the original Framingham Eye Study (1977) which found a prevalence of POAG in an aged population of 3.3%.

Trabecular Changes in POAG

- Specificity of some of the morphologic changes has been questioned because similar findings have been noted in normal, aged eyes without glaucoma.
- This has led some to speculate that glaucomatous changes in the outflow pathway may represent an accelerated aging process.



- Morphologic alterations in the extracellular matrix of the aqueous outflow system in patients with glaucoma have been described in detail.
- These changes include nodular proliferation of extracellular collagen, fragmentation, and "curling" of the collagen fiber bundles. There is an increase in glycosaminoglycan content but an overall decrease in hyaluronic acid. The endothelial cells lining the trabecular meshwork show "foamy" degeneration with basement membrane thickening
- Ultrastructural changes in the juxtacanalicular tissue—the outermost aspect of the trabecular meshwork believed to be the most likely site of obstruction in glaucoma—have also been described



Gonioscopy

- Under the Shaffer angle grading system each quadrant is given a grade from:-

- 0 is closed (either contact or adhesion)

- I 10-15 degrees

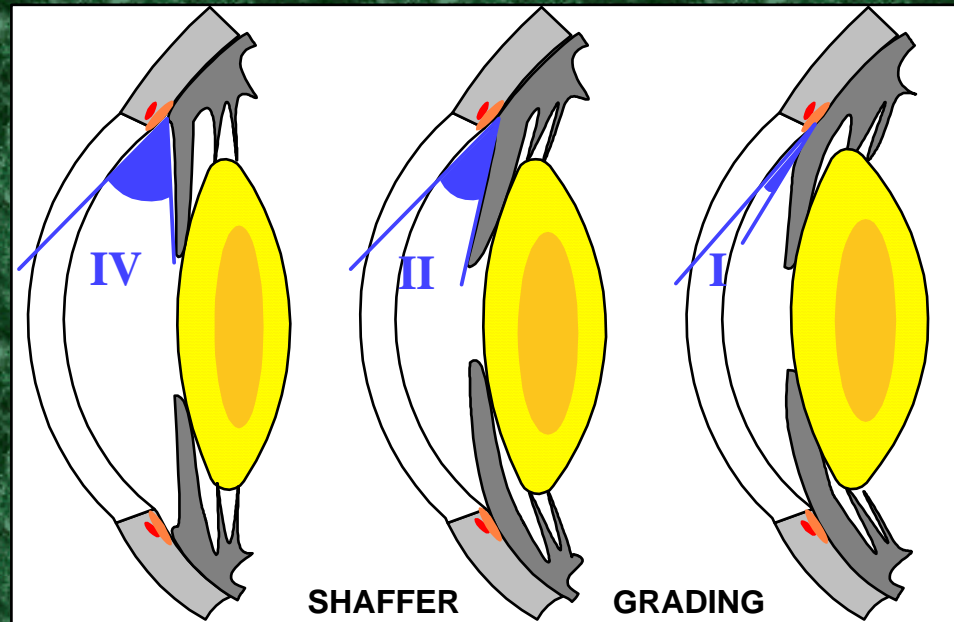
- II 15 to 25 degrees

- III 25 to 35 degrees

- IV 40 or more degrees

- Evaluation includes the assessment of peripheral anterior synechiae (adhesions)

- or any neovascular membranes which can also obstruct aqueous drainage.



Collapse of Schlemm's canal

- Collapse of Schlemm's canal has been invoked as another mechanism of outflow obstruction.
- To support this hypothesis, adhesions between the inner and outer walls of Schlemm's canal have been shown

CELLULAR MECHANISMS OF GANGLION CELL DEATH

There is increasing interest in elucidating the cellular and molecular events that lead to retinal ganglion cell death in glaucoma.

Apoptosis is a process by which excess neurons undergo spontaneous degeneration during normal development. Apoptosis has been demonstrated in primate and rat models of glaucoma. These studies suggest that elevated IOP may trigger cellular events leading to apoptosis. One hypothesis is that elevated IOP impairs the retrograde axonal transport of essential neurotrophic factors and in turn triggers apoptosis of the retinal ganglion cell.



Glutamate and Calcium influx

- Glutamate is an excitotoxic amino acid that normally functions as a neurotransmitter in the retina. Ischemia can produce excess levels of extracellular glutamate, which may lead to cell death through a complex series of cellular events that involves glutamate receptors and Ca^{++} influx into the cell. Elevated levels of glutamate in the vitreous have been demonstrated in glaucomatous monkeys and humans, garnering support for this theory. It is unclear whether the accumulation of vitreal glutamate is a primary or secondary process in glaucoma.

- VASCULAR CONSIDERATIONS
- Proponents of the vascular theory argue that microvascular changes in the optic nerve head are responsible for glaucomatous optic nerve damage. Blood supply to the prelaminar and laminar areas of the optic nerve is derived from the peripapillary choroid and short posterior ciliary arteries.

The vascular supply to the anterior optic nerve may be compromised in glaucoma by several different mechanisms

- :
- 1. The capillary network of the optic nerve head may be selectively lost in POAG
- 2. Hayreh noted the importance of the "watershed" zones of the choroidal blood supply. The watershed zones refer to the border areas between various choroidal segments, each supplied by a short posterior ciliary artery. The watershed zones represent potential areas of compromised circulation and can include the optic nerve head. In addition, nocturnal systemic hypotension has been proposed as an additional risk factor for the development of glaucoma.
- 3. An epidemiologic association between POAG and systemic microvascular disease (e.g., diabetes mellitus) has been reported. Other studies have failed to show a significant correlation between POAG and diabetes.
- 4. There is some evidence that autoregulation of blood flow in the optic nerve head is altered in POAG. Autoregulation is an important mechanism by which arterioles dilate or constrict with the rise or fall in perfusion pressure to maintain constant blood flow to the retina. In glaucoma, this autoregulatory mechanism may be defective and may predispose the optic nerve to ischemic damage.

Myocillin Stop Mutation (TIGR Gene)

- Molecular genetic studies of large families with juvenile open-angle glaucoma have led to identification of the first glaucoma gene (GLC1A) in chromosome 1.27 Interestingly, about 3% of patients with typical adult-onset POAG also have a mutation in the GLC1A gene This suggests gene mutation is responsible for a small but significant portion of POAG. Cellular and molecular events that lead a defective GLC1A gene and cause elevated IOP and glaucoma remain an active area of research.

Genetics of primary congenital glaucoma

- The existence of a hereditary form of PCG segregating as an autosomal recessive trait with high penetrance is now confirmed. The primary molecular defect underlying the majority of PCG cases has been identified as mutations in the cytochrome P450B1 (CYP1B1) gene. This gene is expressed in tissues of the anterior chamber angle of the eye. Molecular modelling experiments suggest that mutations observed in PCG patients interfere with the integrity of the CYP1B1 molecule as well as its ability to adopt a normal conformation and bind haem. CYP1B1 participates in the normal development and function of the eye by metabolising essential molecules that are perhaps used in a signalling pathway.

Transforming growth factors (TGF)

- TGF can inhibit epithelial cell proliferation, induce extracellular matrix protein synthesis, and stimulate mesenchymal cell growth. Elevated levels of TGF- β 2 have been found in the aqueous of glaucoma eyes.
- The study speculated that increased TGF- β 2 levels may be responsible for the decreased cellularity of the trabecular meshwork and may lead to increased debris and resistance to outflow.

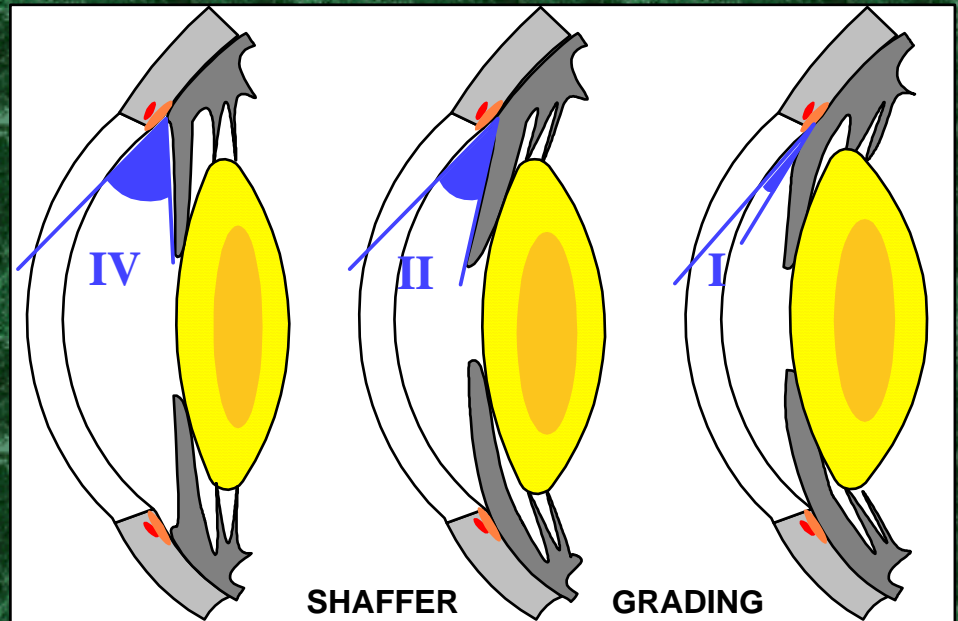
ELEVATED INTRAOCULAR PRESSURE

- The IOP is subject to normal diurnal fluctuation of 3 to 6 mmHg.
- Diurnal variation of more than 10 mmHg is unusual and should raise suspicion for glaucoma.
- The most common diurnal pattern is an early morning peak.
- The early morning peak has been correlated with the endogenous adrenocortical steroid level.

PROGNOSTIC FACTORS

There is evidence that IOP is not only a risk factor for glaucoma but also a prognostic factor. Higher IOP is associated with faster progression of glaucoma.

There is evidence to show that lowering IOP slows or halts progression of the disease



Summary- Classic Risk factors for Glaucoma (POAG)

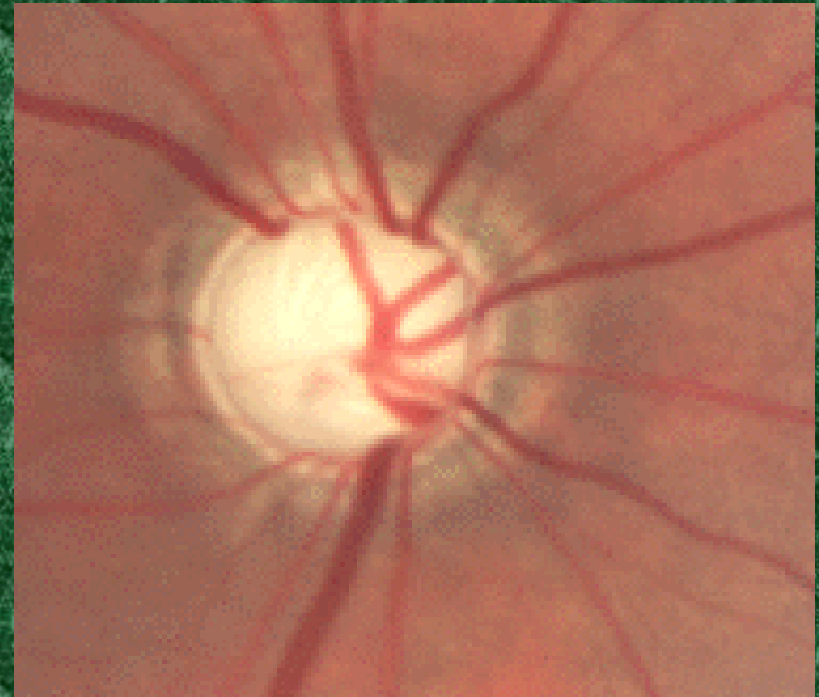
- Strong Association
- Intraocular pressure
- Age
- Ethnicity
- Family History
-
- Moderate association
- Myopia
- Diabetes
-
- Weak Association
- Systemic Hypertension
- Migraine
- Vasospasm

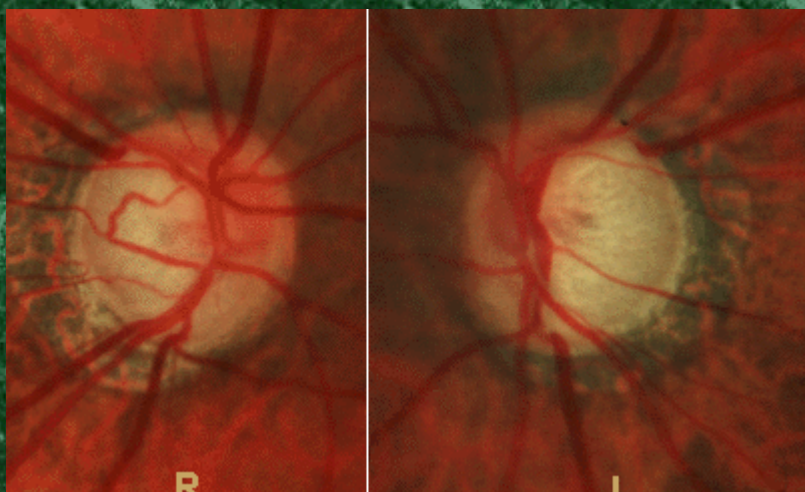
Migraine and Vaso-spasm

- The Blue Mountains Eye Study found a weak association between typical migraine and POAG in one age group (age 70 to 79).
- A Japanese study failed to find any association between migraine and POAG.
- In contrast, association between migraine and normal-tension glaucoma has been reported.
- Ischemia from periodic vasospasm leading to glaucomatous optic nerve atrophy remains an attractive hypothesis.

Optic disc changes in Glaucoma

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- Notching of neuroretinal rim, Pallor, Splinter haemorrhage, Progressive enlargement , vertical elongation, Asymmetry (between the left & right eyes), Nasal displacement of central retinal vessels, baring of lamina cribrosa.
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- Atrophy of the Retinal Nerve Fibre Layer may be detectable using the green (red-free) light of the slit lamp biomicroscope





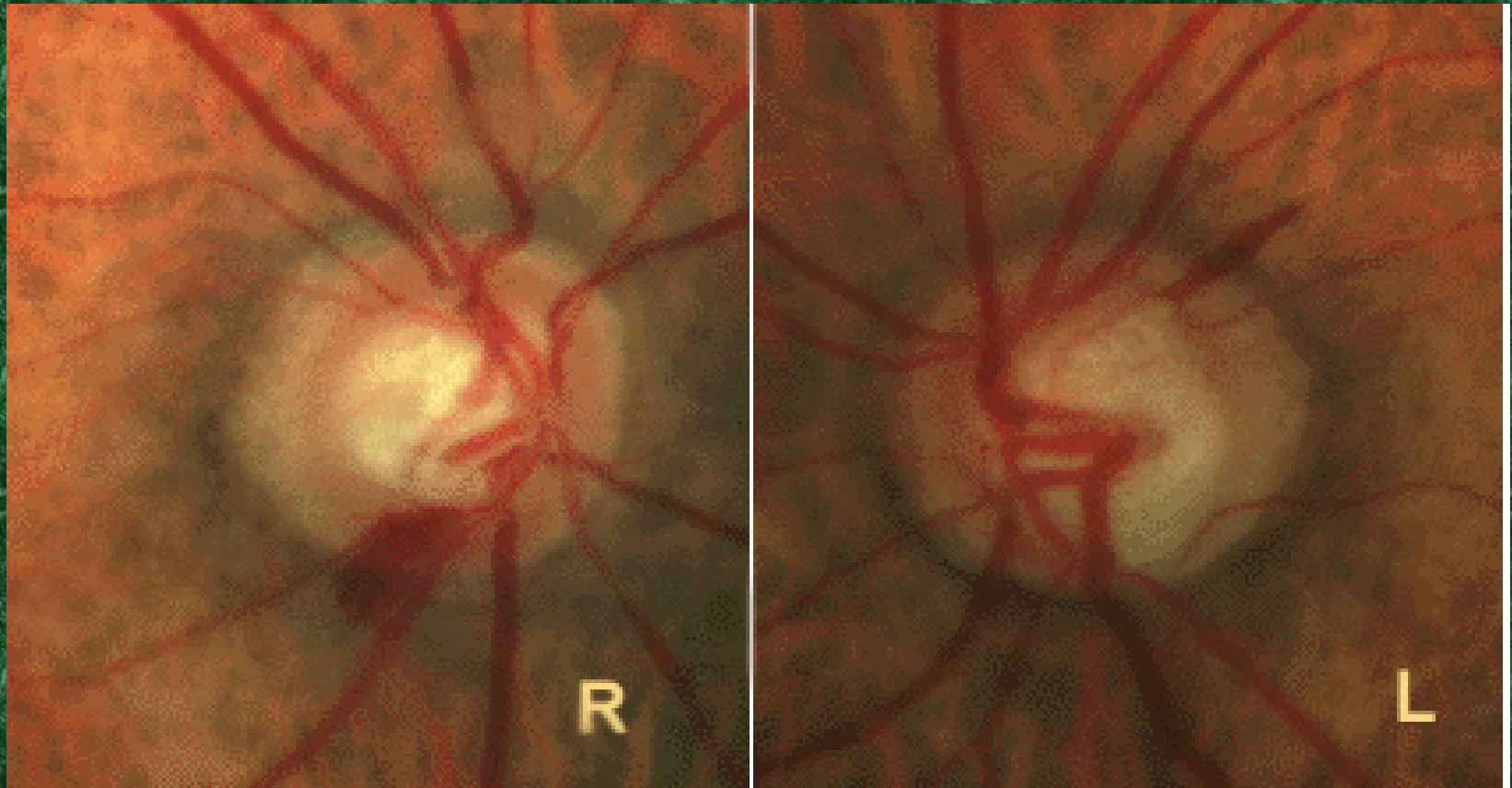
Four different patterns of glaucomatous optic disc changes have been described

- the focal ischemic,
- myopic
- senile sclerotic
- generalized enlargement of the cup.

Prognosis.

- Disc hemorrhage is another important prognostic factor.
- In one study of unilateral disc hemorrhage, the eye with the hemorrhage showed greater visual field progression than the fellow eye.
- A new disc hemorrhage in a patient with glaucoma is considered to be a sign of progressive optic nerve damage.

Disc Haemorrhage



Normal tension glaucoma (NTG)

- Elevated IOP is a major risk factor for the development of glaucoma. However, 20% of patients do not have an elevated IOP.
- It is commoner in females.

A CT scan should be performed before a diagnosis of NTG is made to exclude possible optic nerve compression by a tumour.

NORMAL TENSION GLAUCOMA

Glaucomatous disc and field changes with IOP consistently < 22
20% of newly diagnosed glaucoma patients have IOPs less than 21 mm Hg at presentation.

CAUSE

? Decreased perfusion of disc (arteriosclerosis, low BP)

TYPE

NON PROGRESSIVE-Due to transient vascular shock (single event of systemic hypotension)

PROGRESSIVE- Chronic vascular insufficiency

MIGRAINE ASSOCIATION

CLINICAL

History of CVS disease, diabetes, hypertension / hypotension, steroid use, vasospastic disease (Raynaud's, migraine)

IOP < 22

Large cup relative to field loss

Disc haemorrhage is common.

Field loss closer to fixation and steeper.

INVESTIGATION

Phasing- excludes POAG, shows diurnal range to decide on target IOP

CVS- BP, carotids, ECG, FBC (anaemia), ESR (GCA), cholesterol and triglyceride, BSL

Neuro-exam: CT scan for compressive lesion.

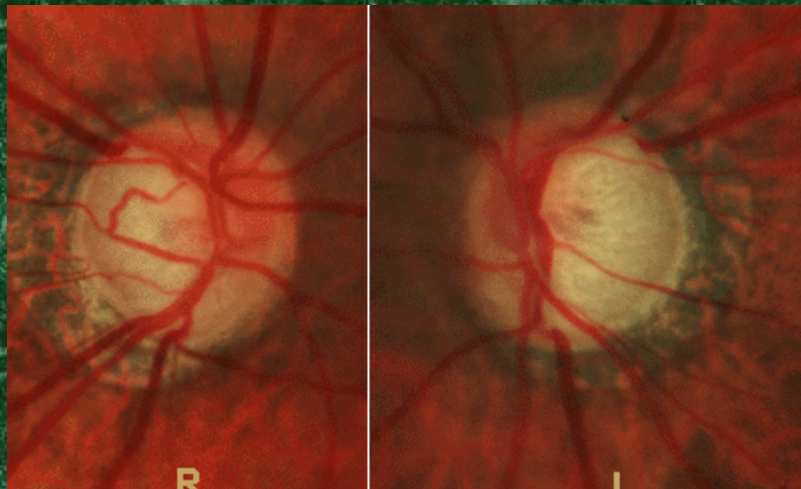
TREATMENT

1. Correct any underlying abnormality such as anaemia
2. Assess for progression and treat only if progression
3. Reduce IOP maximally, aim for 10 mmHg (medical and laser treatment have only a limited role) Often come to surgery:- trabeculectomy + 5FU, Or Scheie thermosclerostomy, rarely a seton. Treat one eye as a therapeutic trial as there is no definite evidence that reducing IOP prevents progression.
4. Consider aspirin and calcium channel blockers for vasospastic disease.

Diagnosis and Management of Primary Open Angle Glaucoma

- *Ocular Hypertension*
- Ocular hypertension can be defined as IOP greater than 21mmHg where the optic disc and visual field are normal.
- The Baltimore Eye Survey, found 6.6% of people had an intraocular pressure greater than 22mmHg in one or both eyes.

Commonly prescribed Anti-glaucoma Eye Drops



- Beta-blockers
- Timoptol (Timolol maleate),
- Levobunolol (Betagan)
- Betaxalol (Betoptic)
- Carteolol (Teoptic)
-
- Other Common Medications
- Brimonidine (Alphagan)
- Dorzolamide (Trusopt)
- Latanaprost (Xalatan)
- Pilocarpine
- Dipivefrin (Propine)

Factors to consider in glaucoma management include-

- Initial IOP
- Life expectancy
- Ethnicity
- Extent of optic nerve damage
- Compliance
-
- A **target** IOP should be determined. This represents the IOP aimed for following therapy. For example, a patient with advanced glaucomatous optic neuropathy may require a target IOP of 12 mmHg.

Diagnosis and Management of Primary Open Angle Glaucoma

- ‘ *Target Pressure* ’
-
- A useful clinical concept is that each eye treated for glaucoma has a target pressure, this is based upon a general assessment of each individual patient’s disease burden.
- 30% to 50% reduction of the pressure at which damage occurs ?

NEUROPROTECTION: POTENTIAL NEW AVENUES FOR GLAUCOMA TREATMENT

The search for neuroprotective agents for glaucoma treatment is grounded in desperation: the desperation of continuing visual loss in some patients despite IOP reduction to quite low levels.

Some possible avenues for neuroprotection

Anti Oxidants

Calcium Channel Blockade

Glutamate Blockade

Anti Apoptosis Agents

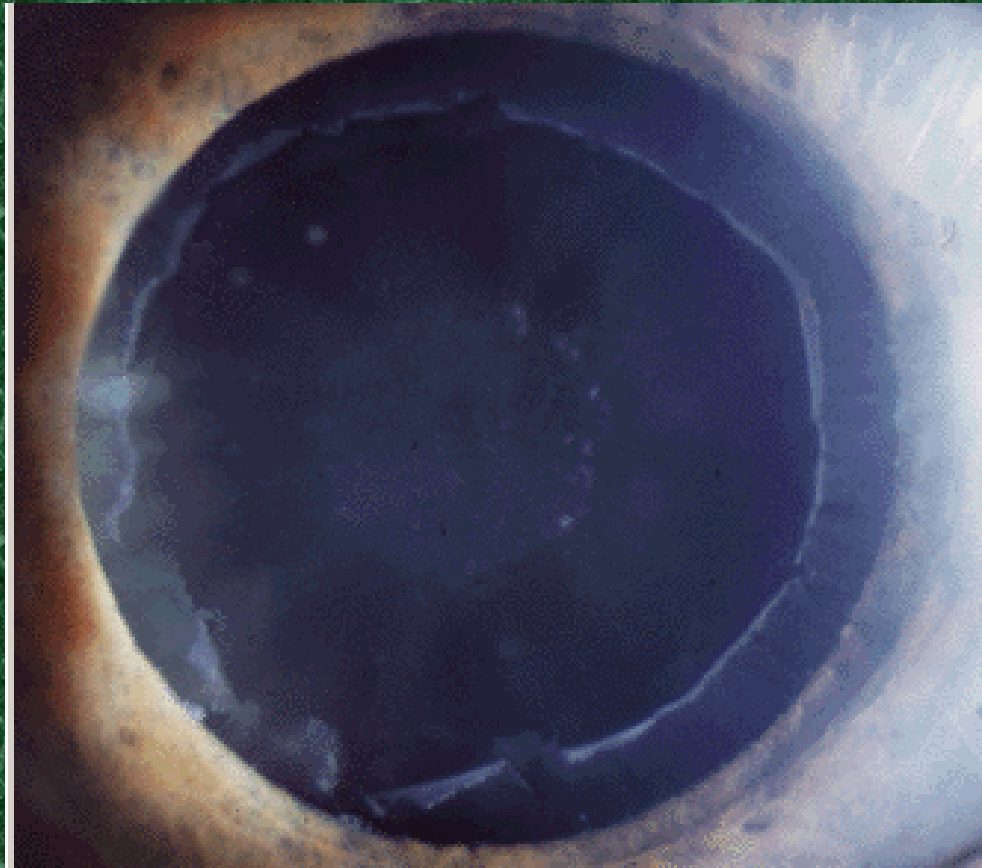
Neurotrophins

Heat Shock Proteins

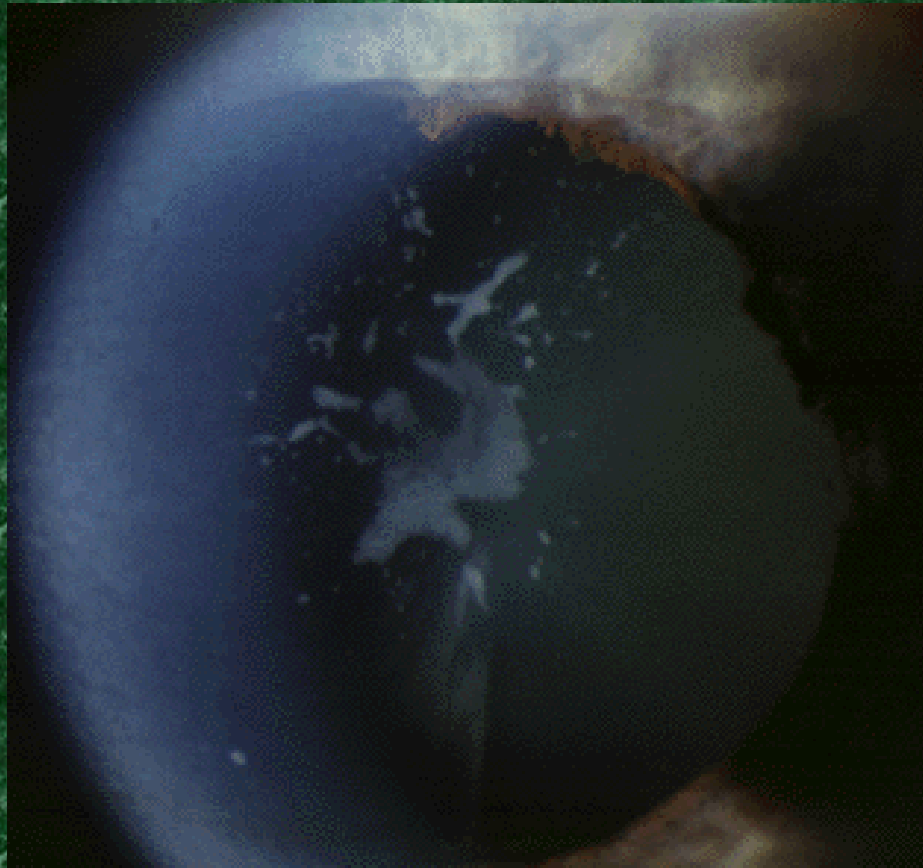
Nitric Acid Synthase Protection

- Royal College of Ophthalmologists stated in 1994
- *‘ patients with POAG comprise approximately 25% of the general ophthalmic workload and half this number as currently diagnosed can be regarded as stable and suitable for a shared care scheme.’*

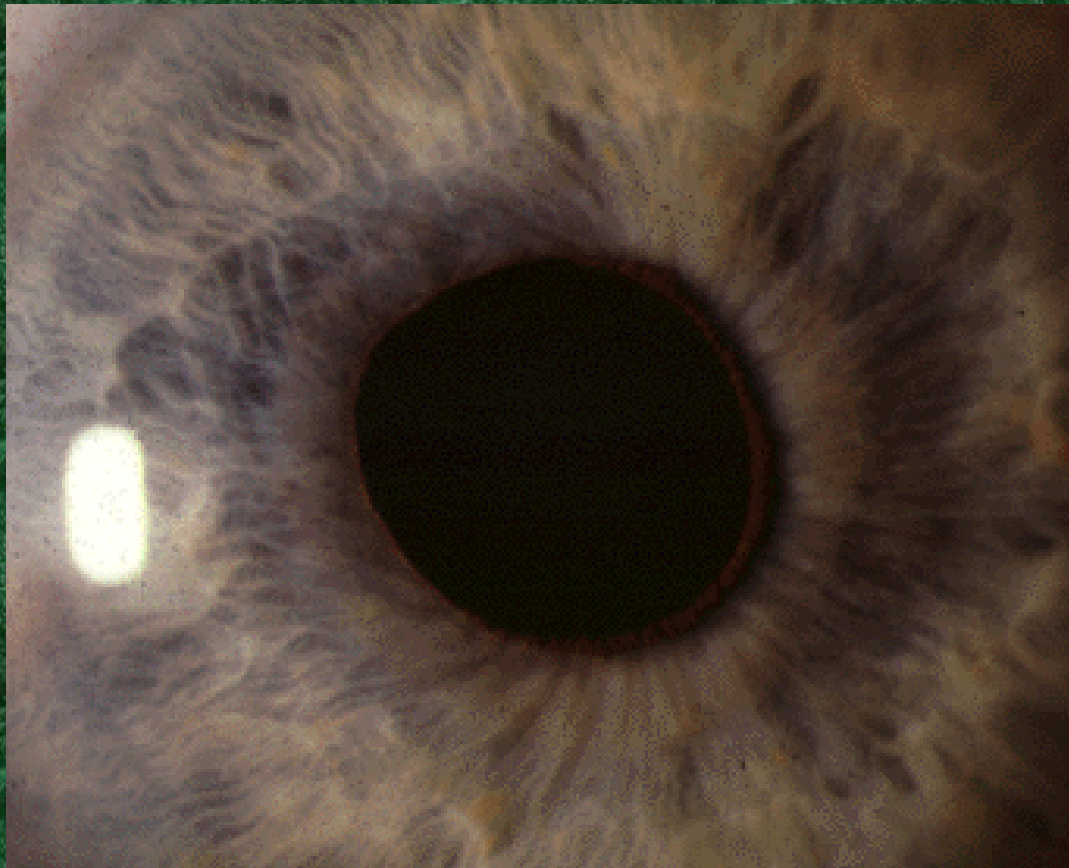
Pseudoexfoliation



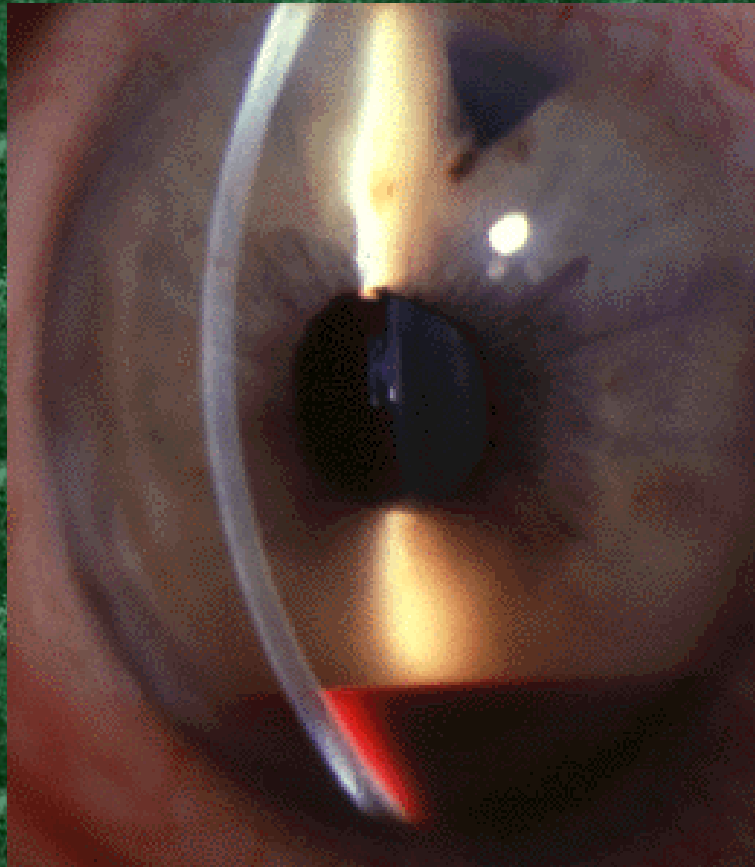
Glaucomaflecken



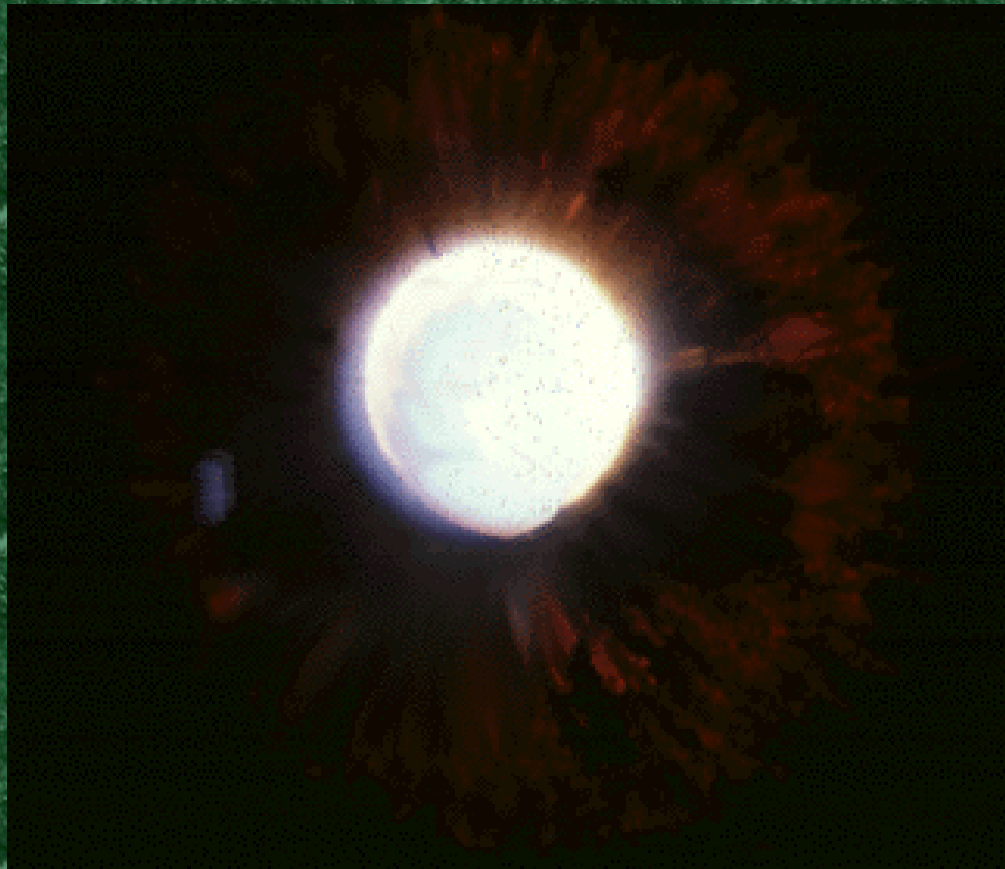
Intermittent Angle Closure



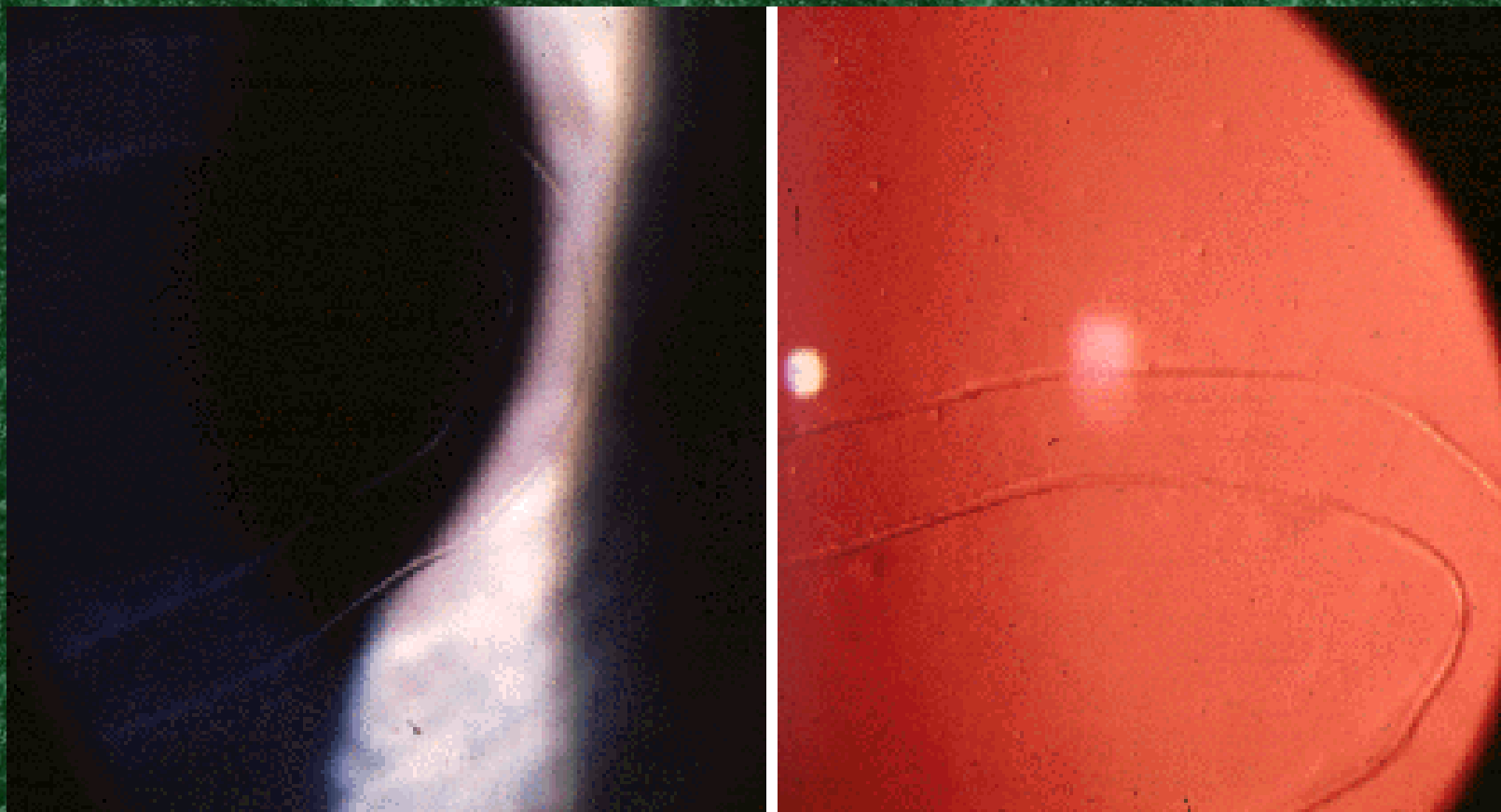
Trabeculectomy



Pigment Dispersion Syndrome



Developmental Glaucoma



Anterior Segment Dysgenesis

