Introduction
The association of glaucoma with uveitis was first described in 1813, by Joseph Beer. The condition was described as 'arthritic iritis', followed by glaucoma and blindness. It still remains one of the most challenging forms of glaucoma to treat, as it is commonly found in younger patients, often has a poor response to topical therapy and unpredictable surgical outcomes. Its impact is not to be underestimated, as it is the commonest cause of visual loss in uveitis patients, after cataract.

Incidence and Prevalence
Accurate incidence and prevalence data are hard to establish. Two key problems exist, firstly study populations are often enriched samples from uveitis clinics, thus creating a bias. Secondly, the diagnosis of uveitic glaucoma is inconsistent and often based on raised intraocular pressure (IOP) alone and not co-existing glaucomatous optic neuropathy.

The overall incidence quoted in the literature is between 10-20%. In a retrospective series of 1099 patients at a single Japanese centre over a 26-year period, 18% were found to have uveitic glaucoma. Their definition of glaucoma was two IOP measurements >21mmHg, requiring treatment.

In a further series of 1254 uveitics, 9.6% developed secondary glaucoma and 6.9% secondary ocular hypertension (OHT). In this series, the term glaucoma was used to describe the presence of pathological optic disc cupping and/or glaucomatous visual field defect with elevated IOP above 21mmHg. In a Scottish centre, the combined incidence of OHT and glaucoma was 11.1% after 5 years amongst 391 uveitics. Another series of 257 uveitics, found a prevalence of 41.8% for OHT and 9.6% for glaucoma. Interestingly, they found no IOP elevation in 58.2% of uveitics.

It may be that the actual incidence and prevalence of uveitic glaucoma is lower than is quoted in the literature, as patients in uveitis clinics tend to have more severe, complex disease and thus may be more prone to raised IOP.

When looking at specific uveitis subgroups, such as Fuchs heterochromic iridocyclitis, glaucoma incidence can be up to 50%.

Pathophysiology and Pathomechanisms
IOP may be reduced or elevated in episodes of uveitis. Reduction in IOP is due to diminished aqueous production and increased uveo-scleral outflow. With increasing chronicity of inflammation, a complex cacophony of mechanisms serves to elevate IOP. Uveitic glaucoma may have open or closed angle mechanism. Anterior segment examination and gonioscopy are an integral part of clinical examination, in determining the mechanism of IOP elevation.

Angle closure in uveitis
The mechanisms of angle closure are outlined in table 1.

Acute Angle Closure mechanisms:
1) Pupil block
This may be absolute pupil block, with 360 degrees of posterior synechiae and total compartmentalisation of the anterior and posterior chambers, with resultant iris bombe. The absolute pupil block is unlike the relative pupil block seen in acute angle closure (AAC), for 4 reasons.

Firstly, clinical examination often reveals a deep central anterior chamber.

Table 1. mechanism of angle closure

| Relative pupil block from fibrin obstructing pupil in severe acute anterior uveitis |
| Absolute pupil block from posterior synechiae |
| Peripheral anterior synechiae (PAS) formation secondary to inflammation (inflammatory nodules in the angle, neovascularisation) |
| Forward movement of lens-iris diaphragm in some forms of scleritis and choroidal effusions |
| Phacomorphic |

Figure 1. Colour photograph showing relatively deep central anterior chamber and shallow periphery in uveitic pupil block. Anterior segment OCT demonstrating shallow anterior chamber and shallow periphery in acute angle closure.
ber, with temporal shallowing, unlike AAC, which tends to have a shallow central and peripheral anterior chamber (Figure 1). Secondly laser peripheral iridotomy (LPI) is often ineffective as a treatment, as the posterior chamber is often not a continuous space in those with secluded pupil, as multiple areas of adhesions can develop between the iris and lens, forming loculations. This is apparent clinically from the asymmetry in the degree of iris bombe (Figure 2a,b). Therefore LPI may resolve bombe in the immediate surrounding area of the PI, but iris bombe will persist in other areas of loculation. Also LPI has a tendency to close in the presence of ongoing inflammation. Thirdly, the iris may remain adherent to the TM and even peripheral cornea in episodes of acute inflammation due to fibrin, so relief of pupil block may not open the angle. Fourthly, absolute pupil block can occur in a pseudophakic eye, unlike PAC, where removal of the lens is the definitive treatment. In cases of secluded pupil, we recommend surgical peripheral iridectomy, viscodissection of posterior synechiae and adhesions between the iris and lens ± goniosynechiolysis as a more definitive treatment.

2) Non-Pupil block – Forward movement of the lens-iris diaphragm
In these cases, cilio-choroidal effusions cause forward movement of the lens-iris diaphragm, with resultant shallowing of the anterior chamber. On clinical examination the anterior chamber is shallower in the centre and periphery, in relation to the other eye. Ultrasound biomicroscopy or B-scan ultrasound can confirm the presence of cilio-choroidal effusions.

Chronic Angle Closure mechanisms:
Peripheral anterior synechiae (PAS) formation
This is common in uveitic glaucoma and often differs in morphology, location and speed of formation in comparison with PAS in primary angle closure (PAC). Conventionally, anatomically narrow angles are more likely to form PAS, however, in uveitics, PAS can also form in wide-open angles. The tendency is to form isolated bridging synechiae or broad PAS, which can then progress to chronic synechial closure (Figure 3).

In our experience, PAS formation occurs preferentially in the inferior angle, as inflammatory deposits gravitate inferiorly. This is in contrast to PAC, where the superior angle tends to be narrowest and therefore, most likely to incur PAS formation. Uveitic PAS formation tends to occur at a faster rate than in PAC. PAS formation is also associated with the presence of large, peripheral iris nodules, such as the Berlin nodules classically in sarcoidosis.

Gonioscopy is key, not only to determine the extent and location of PAS, but also pre-disposing factors for PAS for-
mation, such as inflammatory nodules in the angle, neovascularisation and pigment smudging.

**Open Angle Mechanisms:**

1) Steroid induced trabecular meshwork changes

Steroid responsiveness is seen in 5% of the population and usually occurs 2-6 weeks after steroid commencement, but can occur within days when conventional outflow is compromised. Becker et al. administered betamethasone drops 4 times daily to 26 patients with normal tension glaucoma. By 6 weeks, 92% had IOP greater than 31mmHg and 16 patients had to discontinue their therapy before 6 weeks, as their IOP reached the trial exit IOP of 31mmHg. Armao also found that dexamethasone related IOP elevation was more common in glaucoma patients.

The exact mechanism of steroid induced reduction in outflow facility is not fully understood. Some pathology studies attribute this to alteration in TM ultrastructure, with accumulation of extracellular matrix components, causing reduced outflow. There is also evidence that accumulation of trabecular debris may result from reduced TM phagocytic function.

Debate remains as to whether steroids increase aqueous production. A study looking at aqueous humour production, showed a 42% increase when oral hydrocortisone was administered in combination with intravenous epinephrine. Rice et al. administered Dexamethasone 0.1% 4 times daily for a week to healthy subjects and found that although there was a significant increase in IOP, there was no effect on aqueous production.

Tissue plasminogen activator (tPA), which is responsible for the conversion of plasminogen to plasmin, has been localised in the TM. Plasmin activates matrix-metalloproteases, which play a role in extracellular matrix degradation and maintenance of normal aqueous outflow. Recent work by Kumar et al., suggests that tPA in the TM attenuates steroid induced outflow resistance. There is also evidence that Rho / Rho-associated kinase signal transduction pathway in Schlemm’s canal endothelial cells contributes to steroid induced outflow resistance.

Clinically a steroid induced glaucoma may be elicited by the temporal relationship between commencement of topical steroids and timing of any IOP increase. Gonioscopy findings may allude to the mechanism, as steroid treated uveitics with raised IOP, may have ‘clean angles’ (ie. no pigment smudging) rendering steroid responsiveness as a likely mechanism.

The IOP may take several weeks to return to pre-treatment levels following steroid cessation.

2) Changes to the trabecular meshwork and aqueous – composition in Uveitis

This may be because of mechanical obstruction with cellular debris. Dysfunction of the trabecular lamellae and endothelium may also cause outflow resistance.

In normal eyes, the aqueous protein content is approximately 1% of serum protein. In uveitis, the aqueous protein concentration dramatically rises, giving increased aqueous viscosity and thereby resistance to outflow.

**Predispositions and underlying diseases (immunogenetic inflammatory component)**

Certain uveitis subgroups are at greater risk of developing raised IOP; these include Posner Schlossman syndrome, Fuchs heterochromic iridocyclitis and Herpes simplex keratouveitis. In our experience, conditions with a predisposition for hypertensive uveitis and minimal anterior chamber inflammation tend to get the highest elevations in IOP and those with marked inflammation, do not have such extreme elevation. A possible explanation may be that in severe inflammation, the trabeculitis and TM dysfunction is off-set by ciliary body shutdown. In those with minimal inflammation, there may only be trabeculitis, with little or no effect on the ciliary body.

It remains uncertain whether those with anterior uveitis are more likely to develop raised IOP or not. In the series by Merayo-Lloves two-thirds of patients with uveitic glaucoma had anterior uveitis and Takashi et al. found 73% of patients had active anterior uveitis, when the IOP was elevated. Both Neri and Herbert found no correlation between the location of uveitis and raised IOP.

The presence of chronic uveitis is more likely to be associated with raised IOP, than acute uveitis. Older age and number of years since diagnosis of uveitis have also been significantly correlated with raised IOP.

**Underlying Diseases**

For comments on Posner Schlossman Syndrome, Fuchs’ Heterochromic Iridocyclitis, Herpes Simplex/Zoster Varicella Virus and Juvenile Idiopathic Arthritis please see our Clinical Issues and Practical Tips sections. In addition there are:

Behcet’s Disease (BD)

BD is a chronic occlusive vasculitis affecting both arteries and veins. Ocular involvement is common. In a Turkish series of 129 BD patients, 10% developed secondary glaucoma. Interestingly, in a series of 55 patients, 70% had no active inflammation, in the presence of raised IOP. Mechanisms of raised IOP include open angle mechanisms, steroid therapy, chronic synechial closure, seclusio pupillae and angle neovascularisation.

**Sarcoidosis**

This is a non-caseating granulomatous condition affecting all parts of the body. Several reports have found it to be the leading cause of posterior segment uveitis, to cause glaucoma. Mechanisms include open angle, steroid therapy, chronic synechial closure, seclusio pupillae and angle neovascularisation. Approximately 20% have glaucoma.

**Sarcoid NVG, is known to develop in**

the absence of retinal ischaemia. This is a non-caseating granulomatous condition affecting all parts of the body. Several reports have found it to be the leading cause of posterior segment uveitis, to cause glaucoma. Mechanisms include open angle, steroid therapy, chronic synechial closure, seclusio pupillae and angle neovascularisation. Approximately 20% have glaucoma.

**Tuberculosis**

TB is a caseating granulomatous condition affecting all parts of the body. The mechanism resulting in raised IOP and glaucoma are similar to BD and sarcoid. In an East African series, 25% of blindness secondary to TB, was due to glaucoma.

**Vogt-Koyanagi-Harada syndrome**

VKH causes a bilateral chronic granulomatous panuveitis with associated neuro-logical, auditory and intregumentary manifestations. It commoner in women, and typically affects those in their 3rd – 4th decade. In a series of 101 VKH patients, 29% developed glaucoma. Non-pupil block angle closure secondary to...
cilio-choridal effusions is an important mechanism of raised IOP to recognise in these cases, as the treatment is immunosuppression. It can be misdiagnosed as acute angle closure, distinguishing features include; marked reduction in visual acuity, out of proportion to the corneal oedema and cataract and only moderate elevation of IOP, despite extensive angle closure.29

Syphilis

Syphilis currently poses a significant public health problem, with dramatic increases in incidence in UK, USA and Europe. Uveitis responds well to treatment. It rarely presents with raised IOP, but generally resolves with the treatment of ocular syphilis.

Toxoplasmosis

Ocular toxoplasmosis is characterised by marked inflammation and elevated IOP. The International ocular toxoplasmosis research group found that 30% of 210 patients had elevated IOP.30 This was associated with increased anterior chamber inflammation (p≤0.001) and with macular involvement (p=0.009). In a retrospective review of 61 patients, 38% had elevated IOP. Fifty percent had an IOP >30mmHg, 30% >40mmHg and 10% had IOP >50mmHg. Coincidentally, 7% had lowering of IOP at presentation. OHT resolved with steroid therapy.

Conclusions

Glaucoma is a significant and visually disabling consequence of uveitis. It requires regular assessment of intraocular pressure, gonioscopy and optic disc for its detection. These cases are complex; best management might involve uveitis and glaucoma specialists.
References


