Drug-induced Glaucoma

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Introduction

Glaucoma is a form of optic neuropathy with specific visual field loss. It is usually associated with raised intraocular pressure (IOP). Several drugs have the potential to cause raised IOP; this can occur via an open-angle or a angle-closure mechanism. One of the most important drugs is steroid. Steroid-induced glaucoma is a form of open-angle glaucoma. It is usually associated with topical steroids. However other forms of administration such as inhaled, oral, intravenous, periorcular and intravitreal, can also lead to raised IOP. Medications for treating a variety of systemic conditions including depression, allergies, Parkinson disease etc., can produce pupillary dilation and precipitate an attack of acute angle-closure glaucoma in anatomically predisposed eyes that have narrow angles.

Mechanisms of IOP Elevation in Drug-induced Glaucoma

Open-angle

Steroid is a group of drugs that may produce IOP elevation by open-angle mechanism. Not all patients taking steroid will develop glaucoma. Risk factors include preexisting primary open-angle glaucoma, a family history of glaucoma, high myopia, diabetes mellitus and young age. It has been shown that 18-36% of the general population and 46–92% of patients with primary open-angle glaucoma respond to topical ocular administration of corticosteroids with an elevation of IOP, usually within 2–4 weeks after therapy has been instituted. Topically applied eyedrops, topically applied creams to the periorbital area and intravitreal injections are more likely to cause IOP elevation. The incidence of elevated IOP is less with intravenous, parenteral and inhaled routes of administration. Since IOP elevation can be gradual and asymptomatic, patients on chronic corticosteroid therapy can remain undiagnosed, which can result in glaucomatous optic nerve damage.

Steroid-induced IOP elevation typically occurs within a few weeks after commencing steroid therapy. In most cases, IOP returns spontaneously to the baseline within a few weeks to months upon stopping the steroid. In rare situations, the IOP remains high that requires prolonged glaucoma medication or even surgery.

Closed-angle

Some drugs have contraindications or adverse effects concerning with acute angle-closure glaucoma. These drugs will incite an attack in those individuals with very narrow anterior chamber angles that are prone to occlusion especially when the pupils are dilated. The classes of medications that have the potential to induce angle-closure are topical anticholinergic or sympathomimetic pupil dilating drops, tricyclic antidepressants, monoamine oxidase inhibitors, antihistamines, antiparkinsonism drugs, antipsychotic medications and antispasmodylic agents.

Sulfonamide-containing medications may induce angle-closure glaucoma by a different mechanism, involving the anterior rotation of the ciliary body. Typically, the angle-closure is bilateral and occurs within the first few doses. Patients with narrow or wide open angles are potentially susceptible to this rare and idiosyncratic reaction.

Pathophysiology of Drug-induced Glaucoma

Open-angle

The exact pathophysiology of steroid-induced glaucoma is unknown. It is known that steroid-induced IOP elevation is secondary to increased resistance to aqueous outflow. Some evidence shows that there could be increased accumulation of glycosaminoglycans or increased production of trabecular meshwork-inducible glucocorticoid response (TIGR) protein, which could mechanically obstruct the aqueous outflow. Other evidence suggests that the corticosteroid-induced cytoskeletal changes could inhibit pinocytosis of aqueous humour or inhibit the clearing of glycosaminoglycans, resulting in the accumulation of this substance and blockage of the aqueous outflow.

Closed-angle

Aqueous humour is secreted by the ciliary body and circulates through the pupil to the anterior chamber angle. (Fig. 1) The pathophysiology of angle-closure glaucoma is usually due to pupillary blockage, i.e. iris-lens contact at the pupillary border resulting from pupillary dilation. Medications have a direct or secondary effect, either in stimulating sympathetic or inhibiting parasympathetic activation causing pupillary dilation, which can precipitate acute angle-closures in patients with occludable anterior chamber angles. These include adrenergic agonists (e.g.
phenylephrine), β2-specific adrenergic agonists (e.g. salbutamol), noncatecholamine adrenergic agonists (e.g. amphetamine, dextroamphetamine, methamphetamine and phenidimetrazine) and anticholinergics (e.g. tropicamide). Histamine H1 receptor antagonists (antihistamines) and histamine H2 receptor antagonists (e.g. cimetidine and ranitidine) have weak anticholinergic adverse effects. Antidepressants such as fluoxetine, paroxetine, fluvoxamine and venlafaxine have been associated with acute angle-closures. It is believed to be induced by either the anticholinergic adverse effects or the increased levels of serotonin that cause mydriasis.

Sulfa-containing medications result in acute angle-closures in a different mechanism. This involves the anterior rotation of the ciliary body with or without choroidal effusions, resulting in a shallow anterior chamber and blockage of the trabecular meshwork by the iris. Pupillary dilation and a preexisting shallow anterior chamber angle are not necessary. The exact reason causing ciliary body swelling is unknown in susceptible individuals.

Topiramate is a sulfa-containing anticonvulsant. There were reports about patients on topiramate developing acute angle-closures. However, a pilot study was conducted in the Hong Kong Eye Hospital and the Prince of Wales Hospital recently which showed that short-term use of topiramate did not induce asymptomatic angle narrowing. Therefore it was suggested that topiramate-induced secondary angle-closure glaucoma may be an all-or-none phenomenon.

In drug-induced acute angle-closure glaucoma, the symptoms are the same as in primary acute angle-closure glaucoma. These include sudden eye pain, headache associated with nausea and/or vomiting, blurring of vision and halos around bright objects.

Past Ocular History/Past Medical History
History of systemic medical disease, which could require chronic corticosteroid use (e.g., uveitis, collagen vascular disease, asthma, dermatitis) should be elicited.

Patients with preexisting primary open-angle glaucoma, a family history of primary open-angle glaucoma, diabetes mellitus, high myopia, or connective tissue diseases are at greater risk to be steroid responders.

Clinical Assessment for Drug-induced Glaucoma

History
The patient's current medications should be carefully elicited.

Symptoms
With steroid-induced glaucoma, the pressure elevation is gradual. Therefore, there are very few symptoms during the early stage of disease. At a later stage, patients may complain of loss of the peripheral visual field. At the more advanced stage, when the central vision is also affected, patients may complain of blurring of vision.

Visual acuity and refraction
Patients with acute angle-closures have significant drops in visual acuity. Patients with hyperopia are at higher risks for narrow anterior chamber angles.

Gonioscopic examination
Gonioscopy can evaluate the angle anatomy (i.e. open...
or narrow) and to determine whether the angle is occludable during pupil dilation.

**Optic disc evaluation**

Stereoscopic examination of the optic disc is necessary to exclude glaucomatous damage. The signs of glaucoma optic nerve damage include increased cup-to-disc ratio in horizontal and vertical meridians; progressive enlargement of the cup; evidence of nerve fibre layer damage with red-free filter; notching or thinning of disc rim; pallor; presence of haemorrhage; asymmetry between discs; and peripapillary atrophy. **Fig. 3** shows a pink optic disc with normal cup-disc ratio while **Fig. 4** shows a pale glaucomatous disc with increased cup-disc ratio.

**Investigations**

**Perimetry**

Visual Field testing such as Humphrey or Goldman is used to evaluate the severity of optic neuropathy.

**Optical Coherence Tomography (OCT)**

OCT is an optical signal acquisition and processing method. It captures micrometer-resolution, three-dimensional images from within the optical scattering media (e.g., biological tissue). OCT is an interferometric technique, typically employing near-infrared light. It is used to evaluate the retinal nerve fibre thickness around the optic disc in glaucoma patients. Serial scans can be used to demonstrate any progression of disease.

**Ultrasound Biomicroscopy (UBM)**

UBM is an imaging technique that uses high frequency ultrasound to produce images of the eye at near microscopic resolution. This technique is used to evaluate the anterior chamber angle configuration (i.e. open or closed) and the position of the ciliary body (any anterior rotation). **Fig. 5** shows a narrow anterior chamber angle on UBM.

**Anterior Segment OCT (ASOCT)**

It applies the same principle as OCT but it provides images of the anterior chamber including the angle and the lens.

**Treatment of Drug-induced Glaucoma**

**Medical: Open-angle**

If the patient's underlying medical condition can tolerate discontinuation of corticosteroids, then cessation of the medication will usually result in normalisation of IOP.

In the case of topical corticosteroid drops, using a lower potency steroid medication, such as the phosphate forms of prednisolone and dexamethasone, loteprednol etabonate or fluorometholone should be considered. These drugs have a lesser chance of IOP rise, but they are usually not as effective as an anti-inflammatory drug. Topical nonsteroidal anti-inflammatory medications (e.g., diclofenac, ketorolac) are other alternatives that have no potential to elevate IOP, but they may not have enough anti-inflammatory activity to treat the patient's underlying condition.

In the occasional cases in which the patient's IOP does not normalise upon cessation of the steroid or in those patients who must continue to be on corticosteroid medications, topical antiglaucoma medications are considered.

**Medical: Closed-angle**

If the aetiology is because of sulfa-containing medications, the increase in IOP generally will resolve upon stopping the medication. However, severe cases of sulfonamide-induced angle-closure (i.e. IOP >45 mm Hg) may not respond to simply discontinuing the offending medication. These cases may respond to intravenous mannitol.
For other aetiologies of drug-induced angle-closure, they are treated similar to primary acute angle-closure glaucoma by using antiglaucoma medications including topical beta blockers, prostaglandin analogues, cholinergic agonists and often oral acetazolamide.

**Laser treatment**

For open-angle steroid-induced glaucoma, Argon laser trabeculoplasty or selective laser trabeculoplasty can be applied in the absence of ocular inflammation if the IOP is suboptimal with medication.

In closed-angle glaucoma, argon laser peripheral iridoplasty (ALPI) may be applied to deepen the anterior chamber and widen the angle. Laser iridotomy (LI) can be performed to reverse pupillary block or to prevent further pupillary block. Fig. 6 shows evidence of argon laser peripheral iridoplasty (in green) and laser iridotomy (in red).

**Fig. 6. Slit-lamp photo showing argon laser iridoplasty marks (green circles) and an inferior laser iridotomy (red circle)**

**Surgical: Open-angle**

When medical therapy is ineffective in lowering the IOP to target pressure or the patient is intolerant of medical therapy, then surgical therapy is indicated.

In patients whom both medical and laser therapy have failed to lower the IOP adequately, surgical treatment is warranted. Usually, trabeculectomy, a guarded filtration procedure, with or without intraoperative antimetabolites, is the primary procedure. In cases of eyes with active neovascularisation or inflammation, a glaucoma drainage implant may be used as the primary procedure.

**Surgical: Closed-angle**

Trabeculectomy can also be performed with similar indications as open-angle glaucoma. However the surgery is more difficult since the anterior chamber is shallower and the cornea is usually hazier due to the acute IOP rise.

**Prevention of Drug-induced Glaucoma**

**Open-angle**

Unnecessary prolonged use of steroid should be avoided. Ophthalmic evaluation is recommended for patients treated with long-term steroids especially with risk factors such as family history of primary open-angle glaucoma.

**Closed-angle**

Prophylactic laser iridotomy may be performed in patients requiring frequent mydriasis such as frequent fundus examinations for diabetic retinopathy. Medications causing secondary angle-closure are avoided in susceptible individuals as far as possible.

**Conclusion**

The prognosis of steroid-induced glaucoma depends on the duration of the IOP elevation and the control of IOP after diagnosis. Uncontrolled increase in IOP can lead to permanent optic nerve damage and hence permanent blindness. In patients with controlled IOP, the prognosis can be favourable depending on the severity of disease on presentation. Drug-induced IOP rise can be asymptomatic initially especially in open-angle type. General practitioners should be aware of the risk factors for glaucoma before prescribing a drug that has the potential to cause, precipitate or exacerbate glaucoma. Topical steroids can cause IOP rise in susceptible individuals in a fairly short period of time and therefore it is advised that topical steroids should be prescribed by doctors capable of measuring IOP. Whenever in doubt, an ophthalmologist should be consulted.

**References**