Glaucoma is an optic neuropathy with characteristic structural damage to the optic nerve and visual field loss. It is usually associated with raised Intraocular pressure (IOP).

The glaucoma has traditionally been divided on the basis of primary and secondary forms. Drug-induced glaucoma is a form of secondary glaucoma induced by topical and systemic medications. Although most common one is glucocorticoid, but it is not the only one. Drug induced glaucoma is not synonymous to steroid induced glaucoma. There are many other non-steroidal systemic medicines (Table 1) as well as ophthalmic medicines which (Table 2) have the potential to raise IOP, even anti glaucoma drugs.... YES antiglaucoma drugs.

Mechanisms of IOP elevation in drug-induced glaucoma

IOP elevation can occur via an open-angle or angle-closure mechanism (Table 1 and 2).

Open-angle

Corticosteroid is a group of drugs that may produce IOP elevation by open-angle mechanism. Not all the patients taking steroid will develop IOP elevation. The risk factors include preexisting primary open-angle glaucoma (OAG), a family history of glaucoma, high myopia, diabetes mellitus and young age and rheumatoid arthritis.

It has been shown that 18-36% of the general population respond to topical ocular administration of corticosteroids with an elevation of IOP. IOP rises usually within 2-4 weeks after therapy has been instituted. Topically applied eye drops and creams to the periorbital area and intravitreal injections are more likely to cause IOP elevation than intravenous, parenteral and inhaled forms.

Closed-angle

Some drugs may produce IOP elevation acutely by angle-closure mechanism. These are topical anticholinergic or sympathomimetic pupil dilating drops, tricyclic antidepressants, monoamine oxidase inhibitors, antihistamines, anti-Parkinson drugs, antipsychotic medications and antispasmodic agents. These drugs will incite an attack in individuals with very narrow anterior chamber angles that are prone to occlusion, especially when the pupils are dilated.

Idiosyncratic reaction

Sulfonamide-containing medications may induce an angle closure glaucoma (ACG) 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 susceptible to this rare idiosyncratic reaction.

Pathophysiology of Drug-induced Glaucoma (Figure 1)

Open-angle

The exact pathophysiology of steroid-induced glaucoma is unknown. It is known that steroid-induced IOP elevation is...
## Table 1: Non Steroidal Systemic medicine

<table>
<thead>
<tr>
<th>Group</th>
<th>Example</th>
<th>Effect</th>
<th>Type</th>
</tr>
</thead>
<tbody>
<tr>
<td>Antipsychotropic</td>
<td>Perphenazine and Fluphenazine</td>
<td>Anti cholinergic effect</td>
<td>Angle closure glaucoma</td>
</tr>
<tr>
<td>Tricyclic antidepressant</td>
<td>Amitriptyline and Imipramine</td>
<td>Anti cholinergic effect</td>
<td>Angle closure glaucoma</td>
</tr>
<tr>
<td>Non-Tricyclic antidepressant</td>
<td>Fluoxetine and Mianserin</td>
<td>Anti cholinergic effect</td>
<td>Angle closure glaucoma</td>
</tr>
<tr>
<td>Selective serotonin reuptake</td>
<td>paroxetine, venlafaxine, fluvoxamine, citalopram and escitalopram</td>
<td>Anti cholinergic effect Adrenergic activity Mydriatic effect of increased levels of serotonin Suprachiliary effusion</td>
<td>Angle closure glaucoma</td>
</tr>
<tr>
<td>inhibitors (SSRIs)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sedative</td>
<td>Diazepam</td>
<td>Anti cholinergic effect</td>
<td>Angle closure glaucoma</td>
</tr>
<tr>
<td>Monoamine oxidase (MAO) inhibitors</td>
<td>Phenyldiazepine, Tranylcypromine</td>
<td>Anti cholinergic effect</td>
<td>Angle closure glaucoma</td>
</tr>
<tr>
<td>Antihistamines</td>
<td>Orphenadrin</td>
<td>Anti cholinergic effect</td>
<td>Angle closure glaucoma</td>
</tr>
<tr>
<td></td>
<td>Promethazine</td>
<td>swelling of the lens</td>
<td></td>
</tr>
<tr>
<td>Antiparkinsonian</td>
<td>Trihexyphenidyl</td>
<td>Anti cholinergic effect</td>
<td>Angle closure glaucoma</td>
</tr>
<tr>
<td>Antispasmytic</td>
<td>Propantheline, Dicyclomine</td>
<td>Anti cholinergic effect</td>
<td>Open angle glaucoma</td>
</tr>
<tr>
<td>Antibiotics</td>
<td>Cotrimoxazole, Quinine</td>
<td>swelling of the lens</td>
<td>Angle closure glaucoma</td>
</tr>
<tr>
<td>Sympathomimetic</td>
<td>Epinephrine, ephedrine Phylephrine Amphetamine Hydroxyamphetamine</td>
<td>Sympathomimetic activity</td>
<td>Angle closure glaucoma</td>
</tr>
<tr>
<td>Inhalation agents used in COPD</td>
<td>Salbutamol</td>
<td>β2 receptor agonist</td>
<td>Angle closure glaucoma</td>
</tr>
<tr>
<td></td>
<td>Ipratropium</td>
<td>Anti cholinergic effect</td>
<td>Angle closure glaucoma</td>
</tr>
<tr>
<td>Cardiac agents</td>
<td>Disopyramide</td>
<td>Anti cholinergic effect</td>
<td>Angle closure glaucoma</td>
</tr>
<tr>
<td>Anesthetic agents</td>
<td>Preoperative use of Atropine, Scopalmine, and Ephedrine Endotracheal Intubation Succinylcholine, Ketamine and Chloral Hydrate</td>
<td>Anti cholinergic effect laryngeal spasm, coughing, and wheezing increased extra-ocular muscle tone</td>
<td>Angle closure glaucoma</td>
</tr>
<tr>
<td>Anti convulsant</td>
<td>Carbamazepine</td>
<td>Anterolateral rotation of the ciliary body and lens thickening</td>
<td>Angle closure glaucoma</td>
</tr>
<tr>
<td></td>
<td>Topiramate</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anticoagulants</td>
<td>Heparin and low molecular weight heparin e.g. Warfarin</td>
<td>choroidal effusion</td>
<td>Angle closure glaucoma</td>
</tr>
<tr>
<td>Diuretic</td>
<td>Hydrochlorothiazide</td>
<td>Anterolateral rotation of the ciliary body and lens thickening</td>
<td>Angle closure glaucoma</td>
</tr>
<tr>
<td>Botulinam toxin</td>
<td>Botulinam</td>
<td>Pupil dilation through ciliary ganglion</td>
<td>Angle closure glaucoma</td>
</tr>
<tr>
<td>Marijuana</td>
<td>Marijuana</td>
<td>Atropine like effect</td>
<td>Angle closure glaucoma</td>
</tr>
</tbody>
</table>
secondary to increased resistance to aqueous outflow. But the following observations and theories have been reported.

1. Some evidence shows that there could be increased accumulation of glycosaminoglycans producing biological oedema or increased production of trabecular meshwork-inducible glucocorticoid response (TIGR) protein, which could mechanically obstruct the aqueous outflow.

2. 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.

3. Direct physical obstruction of the trabecular meshwork with crystalline steroid particles.

Pathophysiology of Non Steroidal drugs e.g dicyclomine causing open-angle glaucoma are much more varied including the release of pigment during the pupillary dilation with subsequent obstruction of the trabecular meshwork, and a possible increase of inflow during pupillary dilation.

Closed-angle

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.

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. The exact reason causing ciliary body swelling is unknown in susceptible individuals.

Clinical Assessment for Drug-induced Glaucoma

History

The patient’s detailed history regarding systemic illness which could require chronic corticosteroid use like uveitis, collagen vascular disease, asthma, dermatitis should be asked. History of neurological disease and medications should be carefully elicited.

Patient’s risk factor to be steroid responders like preexisting primary open-angle glaucoma, a family history of primary open-angle glaucoma, diabetes mellitus, high myopia, or connective tissue diseases should be elicited.

Symptoms

In drug induced open angle glaucoma, the pressure elevation is gradual. Therefore, there are very few symptoms during the early stage of disease. Some time patient may complain of coloured haloes. 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.

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.

Physical Examination

A complete ophthalmic examination should be performed including:

Table 2: Non Steroidal ophthalmic medicine

<table>
<thead>
<tr>
<th>Group</th>
<th>Example</th>
<th>Effect</th>
<th>Type</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anti glaucoma medicine</td>
<td>Acetazolamide</td>
<td>Anterolateral rotation of the ciliary body and lens thickening</td>
<td>Angle closure glaucoma</td>
</tr>
<tr>
<td></td>
<td>Pilocarpine</td>
<td>anterior movement of the iris-lens diaphragm</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Latanoprost</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mydriatic agents</td>
<td>Tropicamide, Atropine, homatropine and cyclopentolate</td>
<td>Atropine like effect</td>
<td>Angle closure glaucoma</td>
</tr>
<tr>
<td>Anti VEGF</td>
<td>Lucentis (ranibizumab) Avastin (bevacizumab)</td>
<td>increases the amount of fluid within the eye</td>
<td>Open angle glaucoma</td>
</tr>
<tr>
<td>Surgical agents</td>
<td>Viscoelastic agents, silicone oil</td>
<td>Direct obstruction</td>
<td>Open angle glaucoma</td>
</tr>
</tbody>
</table>
Visual acuity, pupil reaction, intraocular pressure measurement, anterior chamber examination for assessment of anterior chamber depth. Signs of other secondary glaucoma such as uveitic, pigment dispersion and pseudoexfoliation glaucoma should looked for. Posterior subcapsular cataract may present in chronic steroid users.

Gonioscopic examination
Gonioscopy for evaluation of 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 (Figure 2) is necessary to document glaucomatous damage. This can be done by slit lamp biomicroscopy (78D & 90D).

Investigations
Perimetry
Visual Field testing such as Humphrey (Figure 3) is used to evaluate the severity of optic neuropathy. Even when optic nerve damage not present, baseline documentation of visual field is essential.

Optical Coherence Tomography (OCT)
OCT is an optical signal acquisition and processing method. It is used to evaluate the retinal nerve fibre thickness around the optic disc (Figure 4) 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 cilliary body e.g. anterior rotation (Figure 5).

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
If the patient’s underlying medical condition can tolerate discontinuation of drugs, then cessation of the medication will usually result in normalization of IOP.

Medical management for Open-angle drug induced glaucoma
In the case of topical corticosteroid drops, using a lower potency steroid medication, such as the phosphate forms of prednisolone, loteprednol or fluorometholone should be considered. These drugs have a lesser chance of IOP rise20,21,22, but they are usually not as effective as an anti-inflammatory drug. Topical NSAID medications can be considered, but they may not have enough anti-inflammatory activity to treat the patient’s underlying condition23,24.
In cases in which the patient’s IOP does not normalize upon cessation of the steroid or in those patients who must continue to be on corticosteroid medications, topical antiglaucoma medications are considered.

Medical management for Closed-angle drug induced glaucoma

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 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 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.

Laser iridotomy is not effective in cases of acute ACG caused by sulfa drug like topiramate because secondary angle closure glaucoma occurs without pupillary block.

Surgical treatment for Open-angle and Closed angle cases

Indication

1. Medical therapy is ineffective in lowering the IOP to target pressure or
2. The patient is intolerant of medical therapy or
3. In patients whom both medical and laser therapy have failed to lower the IOP adequately.

Usually, trabeculectomy, a guarded filtration procedure, with or without intraoperative antimetabolites, is the primary procedure.

In case of posterior subtenon steroid and in intravitreal steroid, vitrectomy is helpful to lower the load of steroid and IOP.

Conclusion

Uncontrolled increase in IOP can lead to permanent optic nerve damage and permanent blindness. 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 whenever in doubt, an ophthalmologist should be consulted. When prescribing such medicines for long term, regular and complete eye checkup should be done.

References