Theme Article

Ocular Effects of Systemic Medications

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Abstract

Systemic medications can give rise to ocular toxicity due to rich ocular blood supply and small ocular mass. These side effects can range from dry eye, keratitis, corneal deposits, glaucoma, cataract to blinding complications as a result of retinal toxicity and optic neuropathy. This review focuses on commonly used drugs, their ocular side effects, some newer drugs and their toxicity. Baseline examination and follow up at regular intervals is necessary for timely recognition of toxicity and discontinuation of these side effects. Recommendations for monitoring for medications with frequent and/or severe adverse ocular effects are discussed.

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Introduction

Eyes are prone to harmful effects of systemic medications due to a rich blood supply and a small mass.[1]

The drug molecules from the systemic circulation can reach the ocular structures by the uveal or retinal vasculature. Thin fenestrated walls of the choroid, sclera and ciliary body acts as a gateway for small lipid molecules which can pass freely across into the aqueous humour and also diffuse into the avascular structures such as the lens, the cornea, or the trabecular meshwork. The common sites of accumulation of these drugs in the eye are the cornea, lens, and retina.

The drug molecules bind to stromal glycosaminoglycans leading to edema and can reduce the transparency of cornea. The drug molecules can bind to the lens proteins leading to its opacification and cataract formation.

Drug deposits in the retina manifest as a loss of pigmentation and accumulation of pigment-laden cells in the outer retinal layers, leading to damage to the photoreceptors and the ganglion cell layer.

Adverse drug reactions can be dose-related, allergic or idiopathic. Dose-related effects are predictable and common with drugs having a narrow therapeutic index. These are commoner in patients with impaired renal, hepatic function, or polypharmacy leading to drug-to-drug interactions. Allergic aetiology may not be dose-related, commoner in patients with allergic tendencies. Prior exposure to the drug leads to sensitization of the patient and subsequent drug exposures may result in different types of allergic reactions. Sometimes adverse drug reactions may be idiopathic. (Table 1) shows commonly used drugs causing ocular side effects.

Table 1: Common drugs implicated for causing various ocular adverse effects

SNo	Drug group	Ocular side effects
1.	Anticholinergic	Dry eye, Angle closure glaucoma
2.	Alpha 1a agonist	Floppy Iris syndrome
3.	Anti arrhythmias	Corneal deposits
4.	Anti coagulants	Ocular bleed
5.	Anti malarials	Retinal toxicity
6.	Anti epileptics	Visual field constriction, nystagmus
7.	Corticosteroids	Cataract, Glaucoma
8.	Anti tubercular drugs	Toxic optic neuropathy
9.	Anti psychotics	Corneal and lenticular pigmentation
10.	Anti neoplastic	Retinal haemorrhages

Specific Drug Groups and Their Side Effects

Anticholinergic Drugs

Drugs with anticholinergic effects such as antihistamines, antidepressants, anticholinergics, diuretics, ß-blockers and antipsychotics are used to treat various systemic disorders like urinary incontinence, overactive bladder, chronic obstructive pulmonary disorder and organophosphate poisoning. These drugs can lead to ocular surface dryness and may require artificial tear supplementation, punctal plugs, or administration of topical cyclosporine for the treatment depending on the severity.

Angle-closure glaucoma might be induced in predisposed patients due to pupillary dilatation induced by the anticholinergic effect. Oxybutynin and other drugs used in the treatment of overactive bladder have resulted in the rise of intraocular pressure (IOP) in individuals with shallow angles, the majority being adult females.[2] These drugs are also used for the treatment of bedwetting in children and for the prevention of catheter induced spasms after hypospadias surgery.[3] Rare cases of acute rise in IOP have been reported in children after oxybutynin use.

(Figure 1) shows a child with anterior synechiae post keratoplasty who presented with acutely raised IOP after oxybutynin usage. Therefore, a high index of suspicion and prompt referral to an ophthalmologist by the paediatrician is required to prevent a sight-threatening rise in IOP in predisposed patients. (Table 2) shows some commonly used drugs which can cause glaucoma in predisposed individuals.

Alpha 1 blocker

Alpha 1 blocker can be selective α_1 blockers (Tamsulosin), and non-selective α_1 blockers e.g. terazosin and doxazosin are used for the treatment of benign prostatic hypertrophy (BPH) in men and bladder problems in women. This drug relaxes the bladder and prostatic smooth muscle making it easier to urinate.

The alpha 1 blocker has a weakening effect on pupillary dilator muscles. This weakening effect along with the strong

Table 2: Shows drugs causing glaucoma

Class of Drug	Example of drug	Mechanism of action
Adrenergic agonist	Ephedrine	Pupillary block
Non catecholamine adrenergic agonist	Naphazoline, Salbutamol	Pupillary block
Anti cholinergics	Ipratropium bromide, Promethazine	Pupillary block
Tricyclic antidepressants (with anticholinergic side effects)	Imipramine	Pupillary block
Serotonin reuptake inhibitor (with anticholinergic side effects)	Fluoxetine	Pupillary block
Sulfa based drugs	Topiramate and Acetazolamide	Ciliochoroidal effusion leading to forward displacement of lens Iris diaphragm

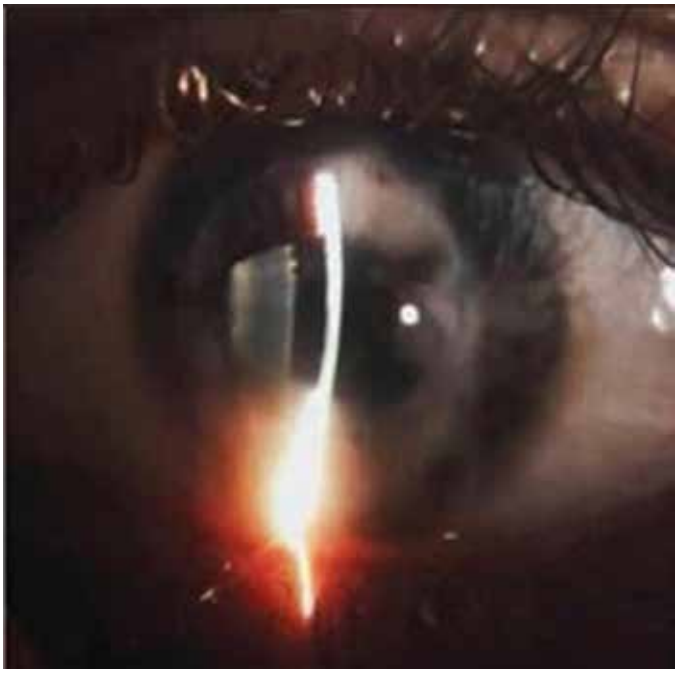

Figure 1: *Showing shallow anterior chamber with synechiae post PK in a child predisposing him to angle closure post oxybutynin (Reproduced from Jain D, Dhua A, Ravisankar V, Chellam L, Joshi M. Acute angle closure glaucoma after hypospadias surgery: A vision-threatening complication of oxybutynin. J Indian Assoc Pediatr Surg 2015 ;20:161-2)*

effect of the constrictor muscle prevents full pupillary dilatation for cataract surgery. In addition, iris billows due to the effect of fluid during irrigation and the atonic muscle tend to prolapse through the main or side port leading to intraoperative floppy iris syndrome (IFIS).[4] It can be graded into mild (only iris billowing), moderate (iris billowing with intraoperative miosis), and severe (moderate IFIS along with iris prolapse). IFIS has also been reported with non-selective agents[5] and has even been reported in patients who have discontinued tamsulosin 1 year back.[6]

Amiodarone

It is used to treat serious cardiac arrhythmias. The patient complains of green halos and also reports a reduction in visual acuity. It can cause vortex keratopathy or cornea verticillata seen as a whorl-like pattern on the cornea. These corneal opacities are not visually significant.

Anterior capsular lens opacities can also be seen and it can lead to multiple chalazia and dry eye. Amiodarone can cause optic neuropathy leading to decreased vision. It appears in 1-2% of the cases and can manifest within a week or two after a patient consumes Amiodarone.

Other drugs that are known to cause vortex keratopathy include chloroquine, Hydroxychloroquine, Amiodarone, Indomethacin, and Tamoxifen.

Anticoagulants

These are used to reduce the incidence of strokes and heart disease. This class of drugs may lead to intraocular and extraocular haemorrhage therefore are usually discontinued prior to surgery. Anticoagulants can also cause retinal haemorrhages. Angle-closure glaucoma due to massive suprachoroidal haemorrhage has been reported post-Warfarin use, so a high index of suspicion is warranted in predisposed individuals.[7]

Antimalarials

They belong to aminoquinolines group e.g., chloroquine and Hydroxychloroquine (HCQ). These are used for the treatment of rheumatologic conditions, malaria etc. With the surgence of coronavirus disease (COVID-19),oral HCQ was administered as a prophylaxis for COVID-19 in the first wave. The retinal toxicity results due to cumulative dosage and concurrent presence of renal disorders and Tamoxifen use.[8] The starting dosage is 400 milligrams to 600 milligrams, a single dose or twice a day. The action of HCQ being cumulative, may require weeks to months, for maximum therapeutic effect for a given patient.

The maximum recommended daily dose of HCQ is ≤ 5.0 mg/kg real weight. For Chloroquine maximum recommended dose is ≤ 2.3 mg/kg real weight.

The risk of toxicity till 5 years is less than 1% and under 2% up to 10 years, but is almost 20% after 20 years. Those who do not manifest toxicity after 20 years have a 4 % risk of toxicity in the subsequent year.

A baseline fundus examination should be done to rule out pre-existing maculopathy. Thereafter annual screening is recommended every 5 years.

Primary screening is performed with automated visual fields plus spectral-domain optical coherence tomography (SD-OCT). Fundus autofluorescence (FAF) can show damage topographically and multifocal electroretinogram (mfERG) provides objective corroboration with visual fields. Modern screening should detect retinopathy before it is visible in the fundus. Retinopathy induced due to antimalarial toxicity is irreversible. Timely recognition and cessation of therapy at an early stage (before any retinal pigment epithelial loss) are important to prevent central visual loss.

Antiepileptic drugs

These are used for the treatment of seizures, as mood-stabilizing agents and treatment of migraine headaches. Vigabatrin irreversibly inhibits Gamma-aminobutyric acid (GABA)-transaminase and is used for refractory seizures in adults and infantile spasms. It can lead to bilateral peripheral visual field constriction

The ocular effects are asymptomatic, the defects may lead to tunnel vision, are largely irreversible and can occur in 30% to 50% of patients after 6 to 24 months of treatment. The recommended safest dose of Vigabatrin is up to 3 g per day in adults, or 50 to 100 mg/kg/day in children. Baseline screening and follow up every 3-6 months is recommended for patients on Vigabatrin. For children under 9 years and who are not cooperative for a visual field examination, follow-up evaluation can be done by means of a fundus examination. Fundus examination in these cases reveals nasal disc atrophy and macular pigmentation. OCT shows thinning of average retinal nerve fibre layer thickness in patients taking Vigabatrin as compared to controls.[10] Electroretinogram (ERG)[11] and Visual evoked potential (VEP)[12] findings may add on to fundus examination for toxicity evaluation. Topiramate toxicity can present with acute myopia, acute angle-closure glaucoma due to anterior chamber shallowing, suprachoroidal effusion, scleritis.[13] Table 3 depicts ocular effects of commonly used antiepileptic drugs

Corticosteroids

Systemic corticosteroids are given orally, nasally, topically, intravenous, intramuscular, and also intraarticular into joints. Oral corticosteroids are the mainstay of treatment of rheumatological disorders, hematopoietic malignancies, bone marrow transplantation, autoimmune disorders, dermatological disease etc.[14]

Corticosteroids can cause posterior subcapsular cataracts, glaucoma[15] and also central serous chorioretinopathy (CSR). Some factors postulated in the development of open-angle glaucoma post corticosteroid therapy are

a) Stabilization of lysosomal membranes leading to accumulation of polymerized glycosaminoglycans (GAGs) in the trabecular meshwork which on hydration increase outflow resistance.[16]
b) Increased expression of extracellular matrix protein fibronectin, laminin, GAG within the trabecular meshwork cells leading to increased trabecular meshwork resistance.[17]
c) Alteration in trabecular meshwork cell morphology by causing an increase in nuclear size and DNA content

The steroid response has classically been described by Armaly and Becker depending on IOP rise.

- High responders (4 to 6% population) – IOP > 31 mm Hg or a rise >15 mm Hg from baseline
- Moderate responders (1/3rd of the population)-developed an IOP between 25-31 mm Hg or rise of 6-15 mm Hg from baseline
- Non-responders (2/3rd of the population) – found to have an IOP <20 mm Hg or a rise of less than 6 mm Hg from baseline

In family members of patients with primary open-angle glaucoma (POAG)and glaucoma suspects risk of ocular side effects increases with chronic use. (Figure 2) shows corticosteroid-induced posterior capsular cataract. (Figure 3&4) Optical coherence Tomography (OCT) and Fluorescein angiography (FA) of steroid-induced CSR.

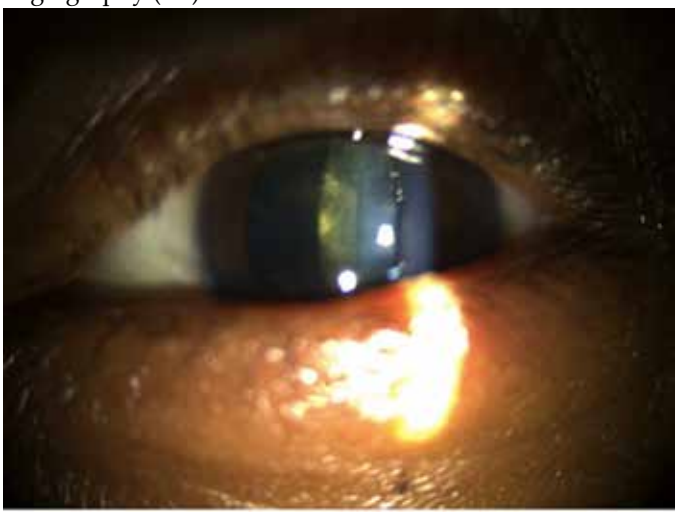

Figure 2: *Corticosteroid induced posterior capsular cataract*

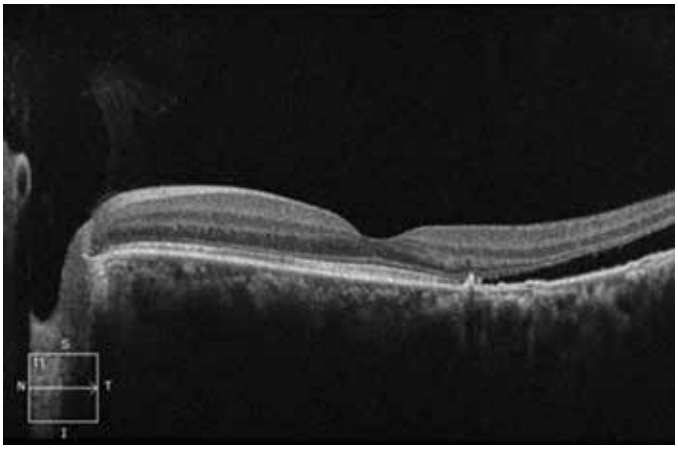

Figure 3: *Showing CSR induced by corticosteroid use (Photo courtesy: Dr Devesh Kumawat, Assistant Professor, Lady Hardinge Medical College, New Delhi)*

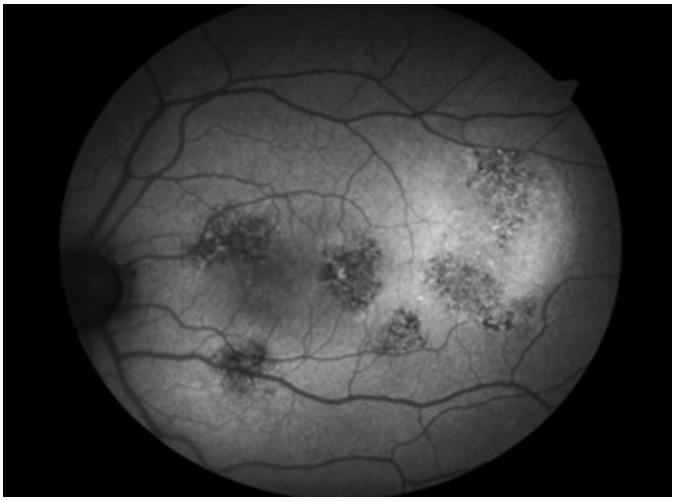

Figure 4: *Multiple leaks seen in a patient of corticosteroid-induced CSR on fluorescein angiography (Photo courtesy: Dr Devesh Kumawat, Assistant Professor, Lady Hardinge Medical College, New Delhi)*

Digoxin

Digoxin is used for the treatment of congestive heart failure and cardiac arrhythmias. Patients with this medication complain of flickering or flashing of light, they can see coloured spots, blue/yellow vision defects and entoptic phenomenon. It is known to cause retrobulbar neuritis. The visual changes due to digoxin are reversible if the drug is discontinued.

Anti-psychotic drugs

These belong to the phenothiazine group e.g. Thioridazine and Chlorpromazine and are used for the treatment of anxiety, depression, and behavioural disorders. These can cause pigmentation of the eyelids, conjunctiva, and even cornea in large doses. Retinal pigmentary degeneration can occur with long term use. It presents as salt/pepper retinopathy leading to widespread loss of retinal pigment epithelium and also choriocapillaris. Drug-induced cataracts can also be induced by antipsychotics. (Figure 5) shows antipsychotic-induced cataract.

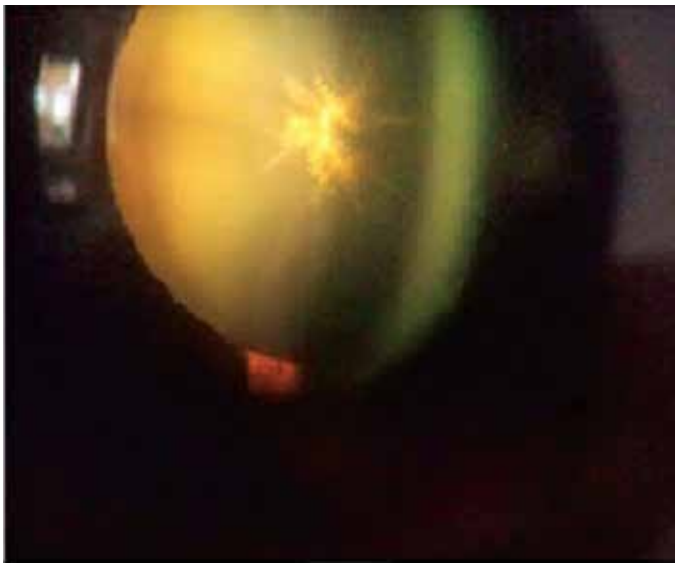

Figure 5: *Chlorpromazine induced cataract (Reproduced from Anterior Segment Involvement in Antipsychotics-An Unusual Presentation. The Official Scientific Journal of Delhi Ophthalmological Society .2018;29 (1), 68-69*

Anti-Neoplastic drugs

Skin hyperpigmentation, epiphora are some common ocular side effects associated with antineoplastic drugs. Interferon A is used for the treatment of hepatitis C and also for the treatment of malignancies, it can lead to retinal ischemia and/or non-perfusion.[18] It can also manifest as optic neuritis and also the dry eye.

Tamoxifen is used for treatment for metastatic breast cancer in postmenopausal women can cause crystalline retinopathy. Methotrexate can lead to peri-orbital edema, blurred vision, photophobia, conjunctivitis, blepharitis, non-arteritic ischemic optic neuropathy. Folate supplementation along with methotrexate, minimizes its adverse effects and may therefore prevent the development of optic neuropathy.

Cytosine arabinoside causes keratitis, especially in high doses. It is said to affect Transient amplifying cells (TACs) located within the basal cell layer of epithelium

Usually occurs with high-dose intravenous therapy >1 g/m2 occurring after 5–7 days of treatment and can be prevented by using topical corticosteroids. (Table 3) depicts ocular toxicity of commonly used anti neoplastic agents.

Biological therapy is recently being used for cancer treatment. These compromise of four groups, molecularly targeted therapies e.g. BRAF inhibitors and MEK inhibitors, Immune checkpoint inhibitors e.g. Ipilimumab, Cytotoxic T-lymphocyte antigen e.g. EGFR inhibitor and others like Bacillus Calmette-Guerin, Ibrutinib etc. Ocular side effects of immunotherapy are uncommon and occur in approximately 1% of patients. The most commonly reported ocular side effects dry eye occurring in 1–24%, inflammatory uveitis in 1%, and myasthenia gravis with ocular involvement.[16]

Table 3: Ocular Toxicity of Anti Neoplastic Agents

Cyclophosphamide	Blurring of vision and dry eye
Cytarabine	Conjunctivitis, keratitis
Fluorouracil	Epiphora, blepharitis, conjunctivitis, cicatricial ectropion
Methotrexate	Epiphora, blepharitis, conjunctivitis, cataracts
Tamoxifen	Retinopathy, corneal opacity, decreased vision
Vinblastine	Extraocular muscle paralysis, diplopia, ptosis
Vincristine	Optic atrophy
Cisplatin and Nitorsoureas	Retinal toxicity and Optic nerve toxicity

Bisphosphonates

Bisphosphonates are prescribed in postmenopausal women to prevent calcium bone loss, these can cause uveitis, orbital inflammation, and scleritis.

Tetracyclines

Tetracyclines, used to treat acne and rosacea can cause idiopathic intracranial hypertension /pseudotumour cerebri, especially with long term use. It can lead to scleral pigmentation in this 3 to 5 mm band starting at the limbus. The skin pigmentations caused by tetracyclines are reversible on discontinuation of the drug. But the eye pigmentation, though less common, is irreversible. (Figure 6) shows papilledema in a patient with pseudotumor cerebri.

Fingolimod

This is used for the treatment of multiple sclerosis. It is known to cause Fingolimod-associated macular edema, commonly known as FAME, sometimes can present with retinal haemorrhages and retinal vein occlusions. Fingolimod-associated macular edema usually occurs within four months of starting treatment. A baseline eye exam and follow up eye exam is required three to four months after starting Fingolimod.

Antiretroviral agents

Cidofovir, is used for treatment for Cytomegalovirus retinitis in AIDS and also as an antiherpetic agent. It can

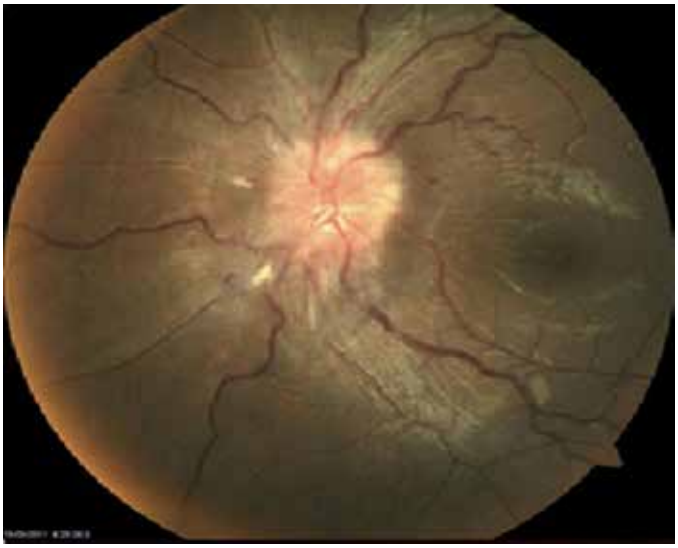

Figure 6: *Papilledema in a patient of tetracycline induced Pseudotumour cerebri*

cause anterior uveitis and can also result in macular folds, retinal or even choroidal detachment, and can permanently impair vision.

Toxic optic neuropathy

An important drug-induced ocular side effect is Toxic optic neuropathy (TON).

The presenting symptom of the patient in toxic optic neuropathy (TON) is bilateral painless loss of vision. TON is dependent on the dose and duration of the offending drug. It has been reported with antituberculosis drugs (Ethambutol and Isoniazid), Antiepileptic Drugs (Vigabatrin), Antimicrobial Agents (Linezolid, Ciprofloxacin, Cimetidine And Chloramphenicol), Disulfiram (in Association with Chronic Alcoholism), Halogenated Hydroquinolones (Amoebicidal Medications), Antimetabolites (e.g. Methotrexate, Cisplatin, Carboplatin, Vincristine And Cyclosporin), Tamoxifen And Sildenafil.

Screening for toxic optic neuropathy includes visual acuity evaluation, color vision, contrast sensitivity and central visual field testing. On Visual fields examination, centroceacal scotoma can be seen, colour vision is impaired. RAPD may not be present; on examination, the disc pallor and optic atrophy ensues.

Ethambutol

Ethambutol chelates metal ions involved in prokaryotic ribosomes. It inhibits arabinosyl transferase, an enzyme in mycobacterial cell wall synthesis.

The ethambutol optic nerve toxicity (EMB) is dose related seen in

- 18% in patients receiving >35 mg/kg/day
- 5-6% with 25 mg/kg/day
- <1% with 15 mg/kg/day of EMB, more than two months
- 4 to 12 months after initiating EMB, but rarely have been reported within a few days of the start of therapy
- Sooner -concurrent renal disease

Even at the "safe" daily dosage of 15 mg/kg, the incidence of ocular toxicity is 1% to 2%. The risk is increased with impaired renal function or diabetes.[19] Bilateral retrobulbar optic neuropathy usually is noted at 3 to 6 months of use, rarely at the start of therapy.[20]

The patient presents with decreased vision and dyschromatopsia. In a study done by Garg et al,[21] the visual loss has been reported in 9.4% of eyes, defective colour vision in 12.3%, 4.7% had optic disc abnormalities and visual field defects were present in 6.3%. Cecocentral scotoma[22] is the commonest visual field defect, but bitemporal defects or peripheral field constriction[23] may also be present. Dyschromatopsia mainly blue yellow, sometimes red-green defects can be the initial symptom in some patients.

OCT show the loss of retinal nerve fibres from the optic nerves, as a sign of early toxicity before fundal findings become manifest. In conjunction with visual field testing this can be used to objectively monitor patients on ethambutol. The majority of defects reverse on timely discontinuation,[24] some reports have noted the persistence of defects due to ethambutol toxicity even after prompt discontinuation of the drug.[25,26]

Reports have pointed out that ethambutol toxicity can even occur with intermittent DOTS therapy[27,21] and complacency in monitoring ocular toxicity can lead to significant ocular toxicity.

Dietary Supplements

Methylsulfonylmethane (MSM) is used as a dietary and detox supplement.[28]. Its use is being recommended due to its anti-inflammatory and antioxidant properties and is currently under trial for effects in arthritis, reduction of seasonal allergies and as an anti-cancer supplement. This being a sulphur compound can lead to angle closure in predisposed individuals secondary to ciliary body effusion.

Conclusion

Systemic drug therapy can have devastating ocular effects if not timely detected. Awareness among physicians and paediatricians prescribing these medications and timely referral to ophthalmologists is the need of the hour.

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