The eye in systemic disease

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Abstract
The eye is a unique organ which is often involved in systemic disease. Patients with systemic disease may first present with eye pathology, and patients with known systemic illnesses may need to have their eyes specifically checked for ocular complications. It is thus useful for the physician to be familiar with the ocular manifestations of common systemic diseases at primary care level. Diseases like diabetes, herpes zoster ophthalmicus and thyroid ophthalmopathy often involve the eyes, and if the eye signs are not identified early, the visual consequences can be devastating. Diabetic retinopathy is an important cause of blindness in this country. These, as well as common ocular manifestations of human immunodeficiency virus/acquired immune deficiency syndrome, syphilis, some dermatological conditions and the ocular side-effects of certain drugs, are discussed in this article. It is important for the primary care physician to be familiar with the spectrum of ocular involvement in systemic diseases since appropriate intervention and referral can be sight saving for the patient.


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Introduction
The eye is a unique organ comprising many different types of tissue. It is often involved in systemic disease. Patients with systemic disease may first present with eye pathology, and patients with known systemic illnesses may need to have their eyes specifically checked for ocular complications. It is thus useful for the physician to be familiar with the ocular manifestations of common systemic diseases at primary care level. The need for an update in this field became apparent after a recent study on the primary health eye care knowledge of general practitioners.1 This article is the fourth in a series which attempts to address this issue.

Approach to the patient
Knowledge of possible eye complications of common systemic diseases will dictate the direction which the eye assessment should take, and the part of the eye on which the examination should focus. Conversely, being familiar with the presenting eye symptoms of certain systemic diseases will facilitate diagnosis, possibly at an earlier stage than would otherwise occur. The diseases to be covered in this article and their ocular manifestations are listed in Table I.

Certain potentially life-threatening systemic illnesses have eye signs which may manifest before other common findings. The more common ones are listed in Table II.

Many systemic drugs cause ocular side-effects, while some ocular drugs have systemic side-effects. Familiarity with these can prevent unnecessary complications (Table III). This list is not exhaustive.

Clinical conditions
Diabetes

Diabetic retinopathy
Diabetic retinopathy is the cause of blindness in approximately 2.5-million of the estimated 50-million blind people in the world. The vision 2020 protocol projects diabetic retinopathy and glaucoma to be the “emerging” causes of blindness in developing countries. Loss of vision in diabetes is most commonly caused by cataracts, vitreous haemorrhage, maculopathy, tractional retinal detachment or neovascular glaucoma.3

Risk factors for the development of diabetic retinopathy include:4
• The duration of diabetes: The most important factor. Duration of disease is the strongest predictor of proliferative diabetic retinopathy.
• Poor control of diabetes: Tight blood glucose control, particularly when instituted early, can prevent or delay development of, or progression to, diabetic retinopathy.
• Pregnancy: Sometimes associated with rapid progression of diabetic retinopathy. Predicating factors include greater pre-pregnancy severity of retinopathy, poor pre-pregnancy control of diabetes, control exerted too rapidly during the early stages of pregnancy, and the development of pre-eclampsia and fluid imbalance.
**Table I: The more common systemic diseases with ocular involvement**

<table>
<thead>
<tr>
<th>Disease</th>
<th>More common ocular manifestations</th>
</tr>
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<tbody>
<tr>
<td>Diabetes</td>
<td>Retinopathy, and third and sixth nerve palsies</td>
</tr>
<tr>
<td>HIV/AIDS</td>
<td>Herpes zoster ophthalmicus, microangiopathy, CMV retinitis, squamous cell carcinoma of conjunctiva and cranial nerve palsies</td>
</tr>
<tr>
<td>Thyroid eye disease</td>
<td>Proptosis, optic neuropathy, lid retraction, restrictive myopathies and soft tissue swelling</td>
</tr>
<tr>
<td>Syphilis</td>
<td>Uveitis, chorioretinitis and optic atrophy</td>
</tr>
<tr>
<td>Rheumatoid arthritis, SLE and other collagen vascular diseases</td>
<td>Scleritis, episcleritis and keratitis</td>
</tr>
<tr>
<td>Ankylosing spondylitis, psoriasis and other seronegative spondyloarthropathies</td>
<td>Uveitis</td>
</tr>
<tr>
<td>Eczema</td>
<td>Keratoconjunctivitis, cataracts and keratoconus</td>
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</table>

AIDS: acquired immune deficiency syndrome, CMV: cytomegalovirus, HIV: human immunodeficiency virus, SLE: systemic lupus erythematosus

**Hypertension:** Tight control (blood pressure < 140/80 mmHg) is particularly beneficial in patients with type 2 diabetes with maculopathy.

**Neopithrophy:** If severe, is associated with worsening of diabetic retinopathy.

Screening for retinopathy in patients with diabetes should take place at puberty in type 1 (juvenile onset) as diabetic retinopathy rarely occurs before then, and at diagnosis for type 2 (adult onset). Fundoscopy (after pupil dilatation) should be performed to detect microaneurysms, retinal haemorrhages (blot or flame-shaped), hard exudates, cotton wool spots, changes in the calibre of the retinal veins and new vessel formation. The classification of retinopathy and primary care management is illustrated in Figure 1, while some of the clinical findings can be visualised in Figures 2, 3 and 4.

The treatment of diabetic retinopathy requires a multidisciplinary approach. Good glycaemic control should be emphasised. Laser photocoagulation is applied to oedematous areas in diabetic maculopathy (to stop blood vessel leakage), and to ischaemic areas in proliferative diabetic retinopathy, in order to decrease the oxygen demand of the hypoxic retina because of thermal damage to it (Figure 5). Complications of proliferative changes include vitreous haemorrhage (Figure 6) from the friable new vessels on the retina or disc, and neovascular glaucoma from the new vessels on the iris growing into the angle and tractional retinal detachment. Retinal surgery is required for nonresolving vitreous haemorrhage and advanced proliferative retinopathy, e.g. traction threatening the macula (Figure 7). New adjunctive therapies in the management of diabetic retinopathy, especially maculopathy, include steroid and antivascular endothelial growth factor agents, both injected into the vitreous cavity. These agents target the inflammatory and neovascular pathways that are involved in the formation of macular oedema and neovascularisation.

Patients with diabetes are also at increased risk of other complications occurring elsewhere, but manifesting with ocular symptoms. Cranial nerve palsies may occur in patients with diabetes. Oculomotor (third) nerve palsy is the most common. It is the result of a microvasculopathy which involves the inner nerve fibres and spares the outer pupillary fibres. If it is complete and the pupil is spared, the patient

**Table II: Systemic diseases, where eye findings may help in making the diagnosis**

<table>
<thead>
<tr>
<th>Disease</th>
<th>Ocular presentation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Myaesthesia gravis</td>
<td>Ptosis and diplopia</td>
</tr>
<tr>
<td>Hyperlipidaemia</td>
<td>Xanthelasma, arcus cornealis and presenile cataract</td>
</tr>
<tr>
<td>Marfan’s syndrome</td>
<td>Myopia, dislocated lens and retinal detachment</td>
</tr>
<tr>
<td>Haematological disease, e.g. anaemia</td>
<td>Retinal haemorrhages, Roth spots and cotton wool spots</td>
</tr>
<tr>
<td>Leukaemia and lymphoma</td>
<td>Uveitis, retinitis, optic nerve infiltration and orbital disease</td>
</tr>
<tr>
<td>Malignant hypertension</td>
<td>Disc swelling, retinal haemorrhages, hard exudates and cotton wool spots</td>
</tr>
<tr>
<td>Albinism</td>
<td>Myopia, astigmatism and nystagmus</td>
</tr>
<tr>
<td>Neurofibromatosis (type 1)</td>
<td>Eyelid neurofibromas and Lisch nodules on the iris</td>
</tr>
<tr>
<td>von Hippel-Lindau disease</td>
<td>Retinal capillary haemangioma</td>
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**Table III: Drugs and the eye**

<table>
<thead>
<tr>
<th>Systemic drugs</th>
<th>Ocular side-effects</th>
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<tbody>
<tr>
<td>Corticosteroids</td>
<td>Cataracts, glaucoma, and worsening of herpetic keratitis</td>
</tr>
<tr>
<td>Ethambutol, isoniazid and streptomycin (anti-tuberculosis)</td>
<td>Toxic optic neuropathy, with loss of central and colour vision</td>
</tr>
<tr>
<td>Chloroquine</td>
<td>Maculopathy, with loss of vision</td>
</tr>
<tr>
<td>Adrenaline and pseudoephedrine (in cold remedies), anticholinergics, antihistamines and atropine</td>
<td>Acute-angle closure glaucoma in susceptible individuals</td>
</tr>
<tr>
<td>Amiodarone</td>
<td>Vortex keratopathy (innocuous corneal deposits)</td>
</tr>
<tr>
<td>Digoxin</td>
<td>Xanthopsia (yellow vision)</td>
</tr>
<tr>
<td>Cidofovir and rifabutin (for HIV)</td>
<td>Uveitis</td>
</tr>
</tbody>
</table>

**Ocular drugs**

<table>
<thead>
<tr>
<th>Systemic side-effects</th>
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<tbody>
<tr>
<td>Beta blockers (drops)</td>
</tr>
<tr>
<td>Acetazolamide (Diamox® tablets)</td>
</tr>
<tr>
<td>Alpha agonists (drops)</td>
</tr>
</tbody>
</table>

HIV: human immunodeficiency virus
should be followed-up regularly for 6-12 weeks, while watching for resolution. If the pupil is involved, compression by an aneurysm or tumour is most likely, and urgent referral for neuroimaging and evaluation by a neurosurgeon is indicated.

Mucormycosis is a rare opportunistic infection caused by fungi which typically affects patients with diabetic ketoacidosis, and is aggressive and often fatal. It involves the sinuses and subsequently spreads to the orbit and brain. These patients require aggressive in-hospital management.

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Human immunodeficiency virus

Herpes zoster ophthalmicus

The varicella zoster virus causes both chicken pox and herpes zoster (shingles). Mechanisms of ocular infection include:

- Direct viral invasion, which may lead to conjunctivitis and epithelial keratitis.
- Secondary inflammation, which may cause episcleritis, scleritis, keratitis, uveitis, optic neuritis and cranial nerve palsies. Inflammation of the eyelid skin and conjunctiva can heal with severe scarring, resulting in a dry ocular surface.

Figure 1: Classification of diabetic retinopathy

Figure 2: Severe nonproliferative retinopathy

Figure 3: Proliferative diabetic retinopathy with new vessels on the retina or elsewhere
• Reactivation, causing inflammation in the affected nerve, and resulting in corneal anaesthesia and neurotrophic keratitis.

The risk of ocular involvement is increased in human immunodeficiency virus (HIV) infection, and also when there is involvement of the skin supplied by the external nasal nerve, a branch of the nasociliary nerve which supplies the tip, side and root of the nose. This is referred to as a positive Hutchinson’s sign, and correlates strongly with ocular involvement and increasing age. It occurs most frequently in the sixth and seventh decades of life. Signs and symptoms are often more severe in the elderly. Herpes zoster ophthalmicus tends to be more severe in patients with HIV. It can also be an early indicator of HIV infection.4,6

A prodromal phase, lasting 3-5 days, precedes the appearance of the rash. It is characterised by malaise, fever and headaches. Some patients may experience burning or tingling in the affected dermatome. The rash is initially erythematous. Groups of vesicles develop within 24 hours, and become confluent over 2-4 days. Vesicles become pustular (Figure 8) before drying after 2-3 weeks.

Treatment includes antiviral therapy with oral acyclovir 800 mg five times daily for 7-10 days. This should be started when the patient first presents. This reduces the severity of the acute episode and the risk of post-herpetic neuralgia. Adequate analgesia should be prescribed to target the neurogenic pain. Amitryptilline or a similar agent should be
used. Skin lesions should be treated with cool compresses and mechanical cleansing. Potassium permanganate dries the lesions well. Blepharitis or conjunctivitis can be treated with topical lubrication. Patients with shingles can transmit chickenpox. Therefore, contact with persons who are not immune, and those with immunodeficiency should be avoided until crusting of the lesions is complete.

All patients with acute herpes zoster ophthalmicus and ocular involvement should be referred for ophthalmic evaluation.

**Human immunodeficiency virus microangiopathy**

This is the most common fundus finding, and is found in more than half of patients with acquired immune deficiency syndrome (AIDS). It is characterised by cotton wool spots, retinal haemorrhages and capillary abnormalities. It is asymptomatic and temporary.

**Cytomegalovirus retinitis**

Cytomegalovirus retinitis is a common ocular opportunistic infection in patients with AIDS. It occurs in patients with very low CD4 T-cell counts (below 50/mm³). Its incidence and rate of progression has declined since the advent of antiretroviral therapy. There are two types of retinitis. The indolent form affects the retinal periphery and progresses slowly. The fulminant type is characterised by a necrotising retinitis, accompanied by a vasculitis, giving a classic “pizza pie” appearance (Figure 9). It is treated with weekly injections of gancyclovir until the retinitis has regressed. Vision will not improve if the optic nerve or fovea is involved. Therefore, early referral within a week is advised.

**Ocular tumours**

Ocular surface squamous neoplasia is a spectrum of benign, premalignant and malignant epithelial lesions of the conjunctiva and cornea. These lesions tend to be unilateral and resemble an atypical pterygium, which grows rapidly, becomes very raised (Figure 10) and keratinised. Besides HIV infection, some other risk factors for development include human papillomavirus type 16 infection and ultraviolet light exposure.

Kaposi’s sarcoma presents on the lid and/or conjunctiva as a flat, bright-red lesion that may mimic a subconjunctival haemorrhage. It responds very well to radiotherapy. Molluscum contagiosum appears on eyelid skin (Figure 11), and can also cause conjunctivitis. It is treated by curettage of the lesions.

**Cranial nerve palsy**

Intracranial infection or inflammation such as tuberculosis or Cryptococcus can often result in cranial nerve palsies. The optic nerve may be primarily or secondarily involved in central nervous system disease. Other cranial nerves that are often affected in HIV infection are the oculomotor (III), trochlear (IV), abducens (VI) and facial (VII) nerves.

**Thyroid eye disease**

Thyroid eye disease affects 25-50% of patients with Grave’s disease, of which 5% have severe involvement. It may precede, coincide with or follow hyperthyroidism, and usually bears no relationship to the severity of thyroid
dysfunction. The major clinical risk factor for developing thyroid eye disease is smoking. The greater the number of cigarettes smoked per day, the greater the risk. Conversely, giving up smoking reduces the risk. Women are five times more likely to be affected by thyroid eye disease than men. Radioactive iodine, used to treat hyperthyroidism, can worsen thyroid eye disease.4

The pathogenesis involves an organ-specific autoimmune reaction which produces inflammation of the extraocular muscles and inflammatory cellular infiltration of the orbital tissues (soft tissue, and fat and lacrimal glands). Clinical manifestations include soft tissue involvement, lid retraction, proptosis (Figure 12), optic neuropathy and restrictive myopathy.4 There are two stages in the development of the disease viz. a congestive (inflammatory) stage in which the eyes are red and painful (tends to remit within three years and only 10% develop serious long-term ocular problems); and a fibrotic (quiescent) stage in which the eyes are not inflamed, but may have a painless motility defect.

The European Group on Graves’ Ophthalmopathy (EUGOGO) severity classification of thyroid eye disease is as follows.9

Mild disease
Mild disease has a minor impact on daily life and is insufficient to justify immunosuppressive or surgical treatment. This group is characterised by:

- Mild soft tissue involvement.
- Mild lid retraction < 2 mm.
- Proptosis < 3 mm.
- No diplopia, nor optic neuropathy, nor signs of corneal exposure.

Moderate to severe disease
Moderate to severe disease is non-sight threatening, but has sufficient impact on daily life to justify immunosuppressive therapy.

Severe disease
Severe disease includes optic neuropathy and/or corneal breakdown.

Management depends on the severity of disease and is often controversial. EUGOGO suggests the following:

- **Mild disease**: Lubricants must be used. Elevate the head of the bed, use ice packs and give selenium 200 µg/day (an antioxidant is needed for conversion of T4 to T3).10
- **Moderate disease**: Immunosuppressive therapy should be employed, using a systemic steroid for 6-12 weeks (radiotherapy may be included).
- **Severe disease (sight threatening)**: A systemic steroid, followed by orbital decompression if there is no improvement having taken the steroid.

Cosmetic surgery to the orbit, eyelids and muscles can be considered once the disease is in the quiescent phase.

**Syphilis**

Syphilis is regarded as “the great mimicker” and has been implicated in a variety of ocular pathologies. It has been associated with chancre of the lid, interstitial keratitis, uveitis and chorioretinitis (Figure 13), as well as optic neuritis and optic atrophy. The eye is considered to be part of the brain, and thus syphilis inside the eye is treated as neurosyphilis with intravenous penicillin for 10 days.2 A lumbar puncture should also be performed to confirm the diagnosis.

**Collagen vascular diseases**

Diseases such as rheumatoid arthritis, systemic lupus erythematosus, Wegener’s granulomatosis and other vasculitic disorders can cause various forms of ocular inflammation. These diseases can be associated with scleritis (Figure 14), episcleritis and immune-mediated
keratitis. Management involves treating the systemic
disease and referral for immunosuppressive therapy for the
ocular condition.

**Seronegative spondyloarthropathies**

Rheumatoid factor-negative and human leukocyte antigen
B27-positive conditions, such as ankylosing spondylitis,
Reiter’s syndrome and psoriasis, are often associated with
a chronic, relapsing non-granulomatous uveitis, which can
be severe. These patients should be referred for ophthalmic
management as they often require intensive topical steroid
therapy and careful follow-up.

**Skin disease**

Atopic conditions, such as eczema, are associated with
atopic (allergic) conjunctivitis, cataracts, keratoconus
and poor resistance to herpes simplex infection. Minor
complaints can be treated symptomatically, but referral is
indicated if vision is reduced. Stevens-Johnson syndrome
and pemphigoid can destroy conjunctival goblet cells and
lacrimal gland orifices, resulting in a very dry ocular surface
and corneal scarring.2 These patients require intensive
lubrication in the acute phase, as well as early referral for
ophthalmic management.

**Systemic diseases where eye findings may help with
the diagnosis**

Many potentially life-threatening systemic illnesses have
accompanying ocular signs which may help with the
diagnosis (Table II). Rapid blood pressure reduction can
result in ischaemic optic neuropathy in patients with
malignant hypertension. Therefore, it is important to reduce
blood pressure gradually during treatment.2 Arcus cornealis
(Figure 15) and xanthelasma in a younger patient can alert
the clinician to hypercholesterolaemia and lead to early
initiation of systemic therapy.

**Drugs and the eye**

Table III lists the important systemic drugs with ocular side-effects and vice versa.

**Conclusion**

Systemic diseases like diabetes, herpes zoster ophthalmicus
and thyroid ophthalmopathy often have ocular involvement,
and if eye signs are not detected early, the visual
consequences can be devastating. Diabetic retinopathy
is the third leading cause of blindness in this country.2
Therefore, it is important for the primary care physician
to be familiar with the spectrum of ocular involvement in
the systemic diseases that have been covered in this
manuscript since appropriate intervention can be sight
saving for the patient.

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**Conflict of interest**

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**References**

among general practitioners in the Cape Town metropole. S Afr Fam Pract.
58-65.
3. Viswanath K, Murray DD. Diabetic retinopathy: clinical findings and management.
5. Diabetic retinopathy study report no. 7: a modification of the Airlie House
7. Richards JC, Maertens G, Davidsie AJ. Course and complications of varicella
zoster ophthalmicus in a high prevalence population (Cape Town, South Africa).
Eye (Lond). 2009;23(2):378-381.
Am Fam Physician. 2002; 66(8):1723-1730
European Group on Graves’ Orbitopathy (EUGOGO) on management of GO. Eur
10. Duntas LH. The role of selenium in thyroid autoimmunity and cancer. Thyroid.
2006;16(5):455-460.