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Editorial

Ocular red flags in systemic diseases: An evidence based overview with recent perspectives

Hannah Ranjee Williams[1*]

[1]Dept. of Ophthalmology, Pondicherry Institute of Medical Sciences, Puducherry, India

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1. Introduction

The eye functions not just for vision, but is an important sentinel which detects systemic disease.[1] It serves as a sensitive window which reflects the status of our body. A wide variety of systemic diseases manifest in the eye, including metabolic, vascular, inflammatory, hematologic, neurologic or drug related. Physicians often refer patients to the ophthalmologist to detect ocular involvement, which may confirm their diagnosis. Oftentimes however, the ophthalmologist may be the physician of first contact for the patient. Prompt recognition of these important ocular signs or 'red flags' may lead to diagnosis of systemic diseases earlier on and prompt systemic evaluation may even prevent serious complications, including visual loss or damage of other organs.

Important 'red flags' have been organized into systemic disease categories as is conventionally done.[2] They have been updated to reflect current understanding as per available literature and diagnostic advances.

2. Endocrine Disorders

Diabetes Mellitus is the leading systemic disease causing ocular morbidity, affecting the eye by metabolic and vascular mechanisms.[3] Chronic hyperglycemia causes damage to the retinal microvasculature, basement membranes, pericytes and nerve fibres, resulting in diabetic retinopathy, cataract, neovascular glaucoma and ocular surface disease.[4] It is not uncommon for the ophthalmologist to be the very first to suspect and diagnose diabetes mellitus as routine screening is not done in many countries, including India. Advances in diagnostics, particularly the non- invasive optical coherence tomography angiography (OCTA) and ultrawide field imaging of the retina had revealed capillary drop out, microaneurysms and microvascular changes sometimes even in the preclinical stages. Early detection and timely intervention (glycemic control, laser photocoagulation, anti-VEGF) remain key to preventing blindness.[5]

Thyroid eye disease (Graves' orbitopathy) is characterised by autoantibody-mediated inflammation, extraocular muscle fibrosis, lid retraction and optic nerve compression. In severe cases, optic neuropathy or exposure keratopathy should be treated as ocular emergencies as they are potentially sight threatening. Between 40–60% of hyperthyroid patients develop ocular signs, and even euthyroid patients may be affected.[6] While proptosis may be uncommon in hyperthyroid states, the latter is the most common cause for proptosis. This underlines the role of the ophthalmologist in thyroid eye disease.

Other endocrine associations — including pituitary tumours and parathyroid disorders — may present with optic neuropathy or chiasmal compression, causing characteristic visual field loss.

*Corresponding author: Hannah Ranjee Williams
Email: drranjee@gmail.com

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3. Circulatory Disorders

It is not uncommon for the ophthalmologists to be the first to diagnose vascular diseases such as hypertension, large-vessel disease, and microvascular / endothelial dysfunction as they may produce a wide spectrum of ocular changes affecting retina, optic nerve, choroid and ocular circulation.

Systemic hypertension, atherosclerosis and thromboembolic disease produce retinal vascular narrowing, hemorrhages, cotton-wool spots and retinal artery and vein occlusions. They may also lead to ischemic optic neuropathy. Retinal vasculature serves as a biomarker for cerebrovascular and cardiovascular disease when analysed using modern automated vessel analysis tools.

Large-vessel vasculitides such as Takayasu arteritis may initially present with retinal ischemia, microaneurysms and neovascularisation, sometimes preceding the systemic diagnosis, so the ophthalmologist contributes significantly to diagnosis and monitoring. The retinal vasculature visualized noninvasively can act as a biomarker for systemic vascular and even neurodegenerative diseases. Newer computational and imaging tools (automated vessel segmentation, quantification of tortuosity, perfusion density metrics) are promising tools which may detect microvascular damage earlier.

4. Rheumatological and Connective Tissue Disorders

All ophthalmologists must have a level index of suspicion to detect autoimmune diseases from the subtle signs they may produce in the eyes. Ocular inflammation occurs in upto 18% of rheumatoid arthritis patients and 90% of patients with Sjogren's syndrome. The typical manifestations include dry eye, episcleritis, peripheral ulcerative keratitis and uveitis. Both scleritis and peripheral ulcerative keratitis which are seen in rheumatoid arthritis patients require aggressive treatment with immunosuppressants, we must be vigilant and ensure early ophthalmic evaluation of these patients, in order to prevent ocular morbidity and help guide systemic therapy while monitoring disease progression. 25-35% of patients diagnosed to have connective tissue diseases such as systemic lupus erythematosus (SLE), antiphospholipid syndrome, giant cell arteritis and polyangiitis have varying degrees of ocular inflammation. Systemic sclerosis often results in ocular surface fibrosis, dry eye and retinal microvascular changes.[7]

5. Neurological Diseases

Systemic neurological disease may affect the vision, pupils and ocular movements. The optic disc is the only cranial nerve which can be visualized non invasively, papilledema alerts us to the disease processes in the brain further emphasizing that the retina is the window to the brain. Due to the common embryological origin of the brain and retina, optical coherence tomography is now being recognised as a biomarker for various diseases such as Parkinson's and Alzheimer's disease. Progressive retinal thinning may precede clinical signs due to neurological disease, which supports the idea of the retina as a window to the brain.[8]

6. Pulmonary Diseases

Diseases of the lungs may initially present to the ophthalmologist. Tuberculosis maybe suspected when a patient presents with a phlycten or granulomatous uveitis.[2] Asthma and COPD alter the systemic inflammatory pathways, resulting in ocular surface inflammation. Sarcoidosis causes uveitis in upto 20%of patients.

7. Gastrointestinal Diseases

The inflammatory bowel diseases such as Crohn's disease and ulcerative colitis are often associated with ocular features, commonly these patients are referred to rule out uveitis, scleritis and episcleritis, all of which may present with acute flare ups of the bowel disease or may occur independently. These ocular signs are being studied for their value as biomarkers.

8. Infectious Diseases

Systemic infections due to bacteria, viruses and parasites may be associated with ocular changes such as conjunctivitis, keratitis, choroiditis and retinitis. Although these signs are often non specific, occasionally as in CMV retinitis, it maybe pathognomonic with no further microbiological tests needed to confirm the diagnosis. Ocular involvement may be the first or only sign in immunocompromised patients, making prompt recognition essential.

9. Skin Diseases

Cicatricial pemphygoid, Stevens- Johnson syndrome, rosacea and atopic dermatitis cause lid margin disease and in severe forms result in conjunctivital scarring and keratitis.[9] Hansen's patients may have ocular involvement in the anterior segment of the eye, ranging from corneal anaesthesia to granulomatous iridocyclitis.

10. Blood Disorders

These often produce tell-tale signs in the eye. Retinal hemorrhages, vascular occlusion and optic nerve ischemia are frequently seen in anemia, leukemia and hyperviscosity states. 'Sea fan' neovascularization seen in sickle cell retinopathy is a key example of this.[10]

11. Malignant Diseases

Malignancies metastasize to the eye, particularly the choroid and occasionally cause paraneoplastic retinopathies. Chemotherapy and radiotherapy produce toxic effects in the eye, so routine eye examination is advised in these patients.

12. Phacomatoses and Genetic Diseases

Neurofibromatosis, Sturge – Weber syndrome and Von Hippel-Lindau disease cause hamartomas of the retina, characteristic vascular malformations and may result in glaucoma. Nowadays, with advanced molecular and genetic testing, we can detect these diseases earlier and advise appropriate treatment.

13. Miscellaneous Conditions

Various metabolic diseases, mucopolysaccharidosis, ectopia lentis and retinopathy of prematurity are diverse systemic diseases which may affect the eye. Their sequelae may be minimal, or result in visual impairment and even blindness. They eye signs might be ambiguous so a high level of clinical suspicion and acumen is required to detect these diseases.

14. Ocular Toxicity from Systemic Drugs

A wide variety of drugs cause ocular side effects. Immunomodulators, chemotherapeutics, and notably antimalarials may result in retinopathy, optic neuropathy and corneal deposits. Lifelong therapy warrants regular ocular monitoring to prevent irreversible toxicity.

15. Conclusion

In conclusion, the eye is a unique and valuable window to the body. Ophthalmic manifestations are often the earliest indicators of systemic disease. A careful examination of the retina, optic nerve, uveal tissues and adnexa may reveal crucial clues to a wide variety of diseases. Many systemic therapies have ocular side effects, underscoring the need for ocular monitoring. Recent advances have strengthened the role of ophthalmology as an essential team player in the management of systemic diseases. Ophthalmologists play a vital role, not only for preserving vision, but in the diagnosis and management of systemic diseases. We should be alert to the systemic associations of ocular findings and examine the patient as a whole, not just ‘rule out the retinopathy’ as referred by Physicians.

A good ‘opportunistic screening’ is vital to detect red flags in the absence of ‘routine screening’ for diseases.

16. Conflict of Interest

None.

References

1. Kanski JJ, Thomas D. *The Eye in Systemic Disease*. 2nd ed. Oxford: Butterworth-Heinemann; 1990.
2. Patton N, Aslam T, MacGillivray T, Deary IJ, Dhillon B. Retinal imaging as a biomarker of systemic disease. *Br J Ophthalmol*. 2005;89(10):1180–1188.
3. Kamboj A, Lause M, Kumar P. Ophthalmic manifestations of endocrine disorders—endocrinology and the eye. *Transl Pediatr*. 2017;6(4):286–99. https://doi.org/10.21037/tp.2017.09.13
4. Cheung N, Mitchell P, Wong TY. Diabetic retinopathy. *Lancet*. 2010;376(9735):124–36. https://doi.org/10.1016/S0140-6736(09)62124-3
5. Spaide RF, Fujimoto JG, Waheed NK, Sadda SR, Staurenghi G. Optical coherence tomography angiography. *Prog Retin Eye Res*. 2018;64:1–55. https://doi.org/10.1016/j.preteyeres.2017.11.003
6. Bartalena L, Gallo D, Tanda ML, Kahaly GJ. Thyroid eye disease: epidemiology, natural history, and risk factors. *Ophthalmic Plast Reconstr Surg*. 2023;39(6S):S2–8. https://doi.org/10.1097/IOP.0000000000002467
7. Kreps EO, Carton C, Cutolo M, Cutolo CA, Vanhaecke A, Leroy BP, et al. Ocular involvement in systemic sclerosis: A systematic literature review, it's not all scleroderma that meets the eye. *Semin Arthritis Rheum*. 2019;49(1):119–25. https://doi.org/10.1016/j.semarthrit.2018.12.007
8. London A, Benhar I, Schwartz M. The retina as a window to the brain—from eye research to CNS disorders. *Nat Rev Neurol*. 2013;9(1):44–53. https://doi.org/10.1038/nrneurol.2012.227
9. Honavar SG. Ocular disease in dermatological disorders. *Indian J Dermatol Venereol Leprol*. 2016;82(5):503–517.
10. Goldberg MF. Natural history of untreated proliferative sickle retinopathy. *Arch Ophthalmol*. 1971;85(4):428–37. https://doi.org/10.1001/archopht.1971.00990050430006

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