Review Article

Ocular Manifestations in Systemic Diseases - A Review

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Abstract

Many systemic diseases have ocular findings that can be seen with flashlight illumination or a direct ophthalmoscope. Many more diseases can be identified with extensive and specialized examination techniques, which are usually not readily available to primary care physicians. However, all physicians can increase their diagnostic accuracy by being aware such signs and symptoms. The corneal manifestations of several selected systemic diseases are reviewed. Metabolic, immunologic and inflammatory and infectious diseases are included. A brief overview of each disease and how it manifests in the cornea is discussed.

Keywords: Ocular manifestations, systemic diseases, blindness, diabetic, neuropathy.

Introduction

Ocular examination is an essential diagnostic component of any physical examination, which can assist in differential diagnosis and be crucial in decision regarding the treatment method [1]. Examples of systemic diseases that may have ocular manifestations include diabetes, hypertension, thyroid disease, multiple sclerosis and myasthenia gravis, amongst many others. Corneal manifestations of systemic disease are numerous, therefore necessitating a biomicroscopic examination of the cornea during any visual examination conducted by an optometrist [2]. Corneal manifestations of systemic disease may be induced by numerous conditions including metabolic, immunologic, inflammatory and infectious processes. The present article reviews selected systemic diseases and the corneal manifestations that may be associated with those diseases [2].

Metabolic Diseases

There are many diseases known to cause ocular or visual changes as a result of systemic disease. Diabetes, for example, is the leading cause of new cases of blindness in those aged 20-74, with ocular manifestations such as diabetic retinopathy and macular edema affecting up to 80% of those who have had the disease for 15 years or more. Diabetic retinopathy is one of the common causes of blindness. It is an ocular manifestation of diabetes, which affects up to 80 percent of all patients who have had diabetes for 20 years or more. Diabetic macular edema is the most common cause of visual dimness in patients with diabetic retinopathy [3]. Other diseases such as acquired immuno deficiency syndrome (AIDS) and hypertension are commonly found to have associated ocular symptoms. Systemic hypertension is a major risk factor for the development of retinal vascular diseases. High blood pressure also increases the risk for including hypertensive retinopathy, retinal vein or artery occlusion, embolic events, the development and progression of diabetic retinopathy. Signs of hypertensive retinopathy are predictive of target-organ damage including cardiovascular and cerebrovascular diseases [4].

High blood pressure affects the heart, kidney, brain, large arteries, and also the eyes. Retinal, choroidal, and optic nerve circulations undergo patho-physiological changes resulting in clinical signs referred to as hypertensive retinopathy, hypertensive choroidopathy, and hypertensive optic neuropathy. Systemic hypertension also increases the risk for the development of retinal vein and artery occlusion, retinal-arteriolar emboli, and diabetic retinopathy. Tyrosinemia II is a rare recessive oculocutaneous syndrome that usually manifests during the early months of life [5, 6]. The disease is associated with bilateral pseudodentdritic keratitis (75% of cases), palmoplantar hyperkeratotic lesions (80% of cases) and mental retardation (60% of cases) [6]. Patients may present with ocular signs and symptoms including epiphora, photophobia, blepharospasm, corneal clouding, pseudodendritic and dendritic lesions and, rarely, corneal or conjunctival plaques [6, 7].

Fabiy's diseases an X-linked fat storage disorder owing to absent (or deficient) activity of lysosomal exoglycohydrolase. Whilst ocular signs may include vascular abnormalities, cataract and vessel tortuosity, the most common, and most distinctive, ocular sign is corneal opacity. The corneal opacities associated with

Fabry's disease are mostly found in the epithelial or sub-epithelial layers of the cornea and present, initially, as a diffuse haziness that progresses to the typical whorl-like corneal verticillata whorl-like rays emanating from a single vortex) [8]. The radial lines are usually cream-coloured but may also range from white to gold en-brown [8]. Cystinosis is a rare autosomal disease resulting in the accumulation of cystine within lysosomes, leading to intracellular cystine accumulations in the conjunctiva, cornea, iris, choroid and retinal pigment epithelium. In the cornea, cystine crystals are predominantly found in the anterior stroma, are iridescent and polychromatic, and needle-like in shape [3]. Photophobia is a common symptom, and the predominantly anterior location of the crystals pre-disposes the cornea to recurrent erosion [3]. Whilst the adult form of the disease is benign, requiring no treatment, the infantile form of the disease can be lethal [5].

Gout is characterized by the deposition of monosodium urate crystals into joints. The disease initially results in transient but recurrent attacks of acute arthritis [9]. The corneal manifestation of gout is the deposition of uric acid crystals into the nuclei of the epithelial cells and the superficial stroma where they appear as fine, punctuate or needle like, retractile crystals [10].

Immunologic Or Inflammatory Disease

Systemic lupus erythematosus (SLE) is an autoimmune disease in which the body's immune system mistakenly attacks healthy tissue in many parts of the body. SLE is a potentially life-threatening multi system disease that is commonly associated with ocular manifestations. Ocular complications have been reported in up to one-third of patients with SLE. Ocular manifestations can be associated with significant morbidity and eye issues may play a role as a marker for systemic disease activity. Kerato conjunctivitis sicca is the most common ocular problem in patients with SLE.

Rheumatoid arthritis (RA) is a 'chronic systemic inflammatory disease of unknown etiology' with the prominent feature being progressive deforming arthritis [9]. Most commonly, keratoconjunctivitis sicca is the ocular disease associated with RA (approximately 15% - 25% of patients) [11].

Sjögren Syndrome (SS) is one of the most frequent systemic autoimmune disorders, mainly involving the eyes and mouth due to inflammation of the lacrimal and salivary glands. Exocrine glands affected with a typical focal lymph ocytic infiltration potentially lead to dry eyes and dry mouth. Calcific band keratopathy (CBK) is considered to be a common condition that is caused by a calcific degeneration of the superficial layers of the cornea (specifically Bowman's membrane, the epithelial basement membrane and the anterior stroma) [12].

This degenerative condition is characterized by deposition of calcium resulting in white-to-grey opacities in the superficial cornea and is usually found in the inter-palpebral zone of the cornea. CKB more commonly starts in the corneal periphery atthe3 and 9 o'clock positions and has a lucent zone that separates the deposition zone from the limbus [13, 14, and 15]. However, chronic ocular inflammatory conditions can result in CBK starting in the central cornea [14].

Sarcoidosis is a granulomatous disease that can include ocular involvement, Steven-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) are rare and sometimes life-threatening hypersensitivity mucocutaneous disease triggered mostly by medications and infections. Major involving tissues are the mucous membranes of oral, gastrointestinal, respiratory, integument and gynecologic tissues. There is no definite effective systemic and local treatment for SJS/TEN. Early detection and aggressive treatment is important for the long-term prognosis of eye. Eyelid margin and palpebral conjunctiva and fornix should be checked thoroughly to detect the cicatrical changes that make chronic ocular surface failure such as limbal cell deficiency and complete ocular surface keratinization. Amniotic membrane transplantation and cultivated oral mucosal graft are benefit to reduce the risk of ocular surface failure. Thyroid Ophthalmopathy (TO) is an autoimmune inflammatory disorder involving the orbit characterized by inflammation and swelling of the extra-ocular muscles and an increase in orbital fat and connective tissue. Current treatments consist of systemic immuno suppression, orbital irradiation, and surgery. It is promising for patient refractory to conventional therapy that pathogenesis of TO at molecular level which advance development of new therapies targeting cellular immunity are now better understood. Future therapies targeting immune system or specific molecules are under investigation and show promise for the future [3].

Infectious Conditions

Systemic infections that are caused by various types of pathogenic organisms can be spread to the eyes as well as to other solid organs. Bacteria, parasites, and viruses can invade the eyes via the bloodstream. Despite advances in the diagnosis and treatment of

systemic infections, many patients still suffer from endogenous ocular infections; this is particularly due to an increase in the number of immuno suppressed patients such as those with human immuno deficiency virus infection, those who have had organ transplantations, and those being administered systemic chemotherapeutic and immune-modulating agents, which may increase the chance of eye involvement [3].

Interstitial keratitis (IK) is 'characterized by cellular infiltration and vascularization of the corneal stroma with minimal involvement of the corneal epithelium or endothelium' [16]. In the acute phase, the signs include vascularisation of the stroma, oedema, hyperaemia and even anterior chamber reaction. Non-acute signs include deep stromal haze, scarring, corneal thinning and ghost vessels in the stroma [17]. With congenital syphilis being the most common cause of IK [17,18], other less common causes include acquired syphilis, tuberculosis, Cogan's disease, leprosy, herpes simplex and Lyme disease [17]. Phlyctenulosis (or phlyctenular keratoconjunctivitis [PKC]) is a 'localized, noninfectious inflammatory process of the ocular surface' [35]. The presence of PKC is thought to represent a delayed hypersensitivity to some antigen - an antigen usually associated with bacteria, mycobacteria, a virus, and protozoan, fungal or parasitic organisms [35]. Systemic diseases such as tuberculosis, Behçets disease, HIV and rosacea are commonly associated with PKC. [17] PKC can present with both corneal and conjunctival phlyctens. Usually, conjunctival phlyctens manifest as small nodules on the bulbar conjunctiva, are white in colour and are often found near the limbus [17]. Corneal phlyctens also present as small, white nodules that often start at the limbus. Dilated conjunctival vessels are often found associated with the nodule. The nodule often migrates towards the centre of the cornea, resulting in a wedge-shaped neovascularised and scarred cornea.

Conclusion

Numerous systemic diseases manifest associated signs in the cornea. In some instances, the corneal changes might be the first indication that some, more serious, disease process underlies the corneal signs. Optometric practitioners need to be alert to the systemic diseases that may present with corneal manifestations.

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