

The cornea in systemic disease

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Abstract

Systemic disease often results in corneal signs that are easily observable by means of biomicroscopy. Optometry is in a unique position to detect the corneal manifestations of systemic disease. This review presents corneal signs of various systemic diseases. The list is not complete but the review rather attempts to emphasize the importance of detection, and referral, of systemic diseases.

Introduction

There are numerous ocular signs and symptoms of systemic disease¹. Vascular systemic diseases that might result in ocular signs include diabetes, hypertension and hyperlipidemia, while autoimmune diseases could include Reiter's syndrome, rheumatoid arthritis and systemic lupus erythematosis. Other disease classifications include metabolic, infectious, nutrition and dermatologic causes of disease. While many of the diseases mentioned above produce changes in the crystalline lens, the retina, extra-ocular muscles and other structures in and around the eye, this review is going to be limited to the corneal manifestations of systemic disease. Optometry is a primary health care profession and as such it is the responsibility of all optometrists to have foundation knowledge of the various diseases that cause corneal changes as well as the actual corneal presentation of the specific disease. The use of biomicroscopy is ubiquitous in optometry making optometry one of the few professions that are able to detect the corneal manifestations of systemic disease on a routine basis.

Metabolic disease

Metabolic disease is defined as: a disease caused by some defect in the chemical reactions of the cells of the body². Corneal manifestations of metabolic disorders occur when a systemic metabolic process results in an accumulation of abnormal substances in the cornea³. The substances that may be deposited in the cornea include proteins, amino acids, carbohydrates, lipids, purine and pyrimidine¹. In many instances deposition of the above mentioned substances occur in asymptomatic patients.

Wilson's disease: also known as hepatolenticular degeneration, is an autosomal recessive disorder that affects the metabolism and excretion of copper⁴. Impairment occurs in the liver's ability to transport and store copper in the bile, a situation that results in accumulation of copper in the liver, central nervous system, cornea and other organs. The manifestations of copper toxicity include⁴: cirrhosis of the liver, hepatitis, rigidity, ataxia, cognitive impairment, affective disorder and psychosis. If untreated the disease is fatal. The corneal manifestation of Wilson's disease is the Kayser-Fleischer ring, a deposition of copper in the periphery of the cornea. The Kayser-Fleischer ring is found in 100% of patients who present with neurologic findings and in 70-90% of those who have liver disease⁴. The detection of the Kayser-Fleischer ring is made much easier by means of a biomicroscope.

Cystinosis: "is a rare disorder characterized by the intralysosomal accumulation of free cystine in the body tissues"⁵. The cause of cystinosis is a defect in the lysosome membrane transport system whereby cystine cannot be removed from lysosomes and delivered into the cytoplasm. The cys-

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Received 3 July 2005; revised version accepted 29 September 2005

tine crystals are deposited in multiple organ sites including the cornea, conjunctiva, bone marrow and internal organs^{5,6}. Three phenotypes of cystinosis have been found: infantile, adolescent and adult and each form of the disease has a different manifestation⁵. Ocular involvement occurs in all three phenotypes of cystinosis with crystal deposition in the cornea (the most common ocular manifestation), conjunctiva, uvea, anterior lens surface and the retina^{5,6}. The crystals are seen as fine, needle-like deposits that are distributed uniformly throughout the cornea. The results of the cystine deposition are: glare disability, changes in contrast sensitivity and light sensitivity. The conjunctival manifestation presents as white deposits with a ground glass appearance. Deposits on the iris increase the potential for posterior synechiae and pupillary block⁶. It is believed that the presentation of crystals of cystine in the cornea present a picture that is unique enough for the diagnosis to be made^{5,6}.

Gout: "is a disorder characterized by sudden, recurring attacks of very painful arthritis caused by deposits of monosodium urate crystals, which accumulate in the joints because of an abnormally high uric acid level in the blood"⁷. With time the acute arthritis attacks eventually lead to chronic disabling arthritis and deposits of urates in other tissues like joint capsules, heart valves and kidney⁸. The most common ocular manifestation of gout is conjunctival injection which is described as dusky red⁹. Crystal and tophi (a chalky white deposit of sodium urate occurring in gout²) deposition in the cornea occurs rarely and presents in the epithelial and sub-epithelial layers. Corneal deposits usually appear as fine, refractile yellow crystals that are found predominantly in the interpalpebral area, very often being confused with band keratopathy³.

Amyloidosis: is the abnormal extracellular deposition of amyloid in various organs and tissues, often in the walls of small vessels². Amyloid appears as an amorphous, hyaline extracellular substance that results in pressure damage to cells adjacent to the amyloid tissue⁸. On a microscopic level amyloid is seen as a fibrous protein with a characteristic fibrillar appearance with an occasional larger rod of material being included in

the meshwork¹⁰. The deposition of amyloid usually occurs in one of two patterns: generalized and local with the generalized form being more common¹⁰. The main organs affected in the generalized form of the disease are: spleen, kidney, liver, intestines, adrenals and the lungs. In the cornea amyloidosis can present as: lattice dystrophy (types I and II), granular lattice, and primary corneal amyloidosis (gelatinous drop-like dystrophy)³. Pavan-Langston¹¹ states that amyloidosis can result in band keratopathy as well.

Fabry's disease: is a sex-linked recessive sphingolipidosis (a general designation applied to diseases characterized by abnormal storage of sphingolipids²) characterized by renal failure, peripheral neuropathy and skin lesions^{3,12}. Generally the disease manifests the following: angiokeratomas (telangiectatic skin lesions), hypohydrosis, corneal and lenticular opacification and vascular disease of the kidney, heart and brain¹². Fabry's disease is different from other sphingolipidoses in that patients have normal intelligence without severe central nervous system ramifications¹¹. The disease also results in excruciating pain in the toes and fingers¹³. A number of ocular changes take place in patients suffering from Fabry's disease including: conjunctival and retinal vascular tortuosity, anterior subcapsular opacities, ocular motility abnormalities and corneal changes. The corneal changes manifest as whorl-like striations that converge in the inferior cornea appearing as white or yellow dots forming a line in the epithelium. Usually the corneal changes are of no significance^{1,3}, however, Berkow⁷ states that the cornea becomes cloudy and that vision is affected.

Immunologic/inflammatory disease

A number of systemic immunologic or inflammatory conditions present signs in the cornea and several conditions will be presented here. Unlike metabolic conditions, immunologic conditions very often result in symptomatology from an ocular point of view.

Rheumatoid arthritis (RA): very often classified as a connective tissue or collagen disease with the following common features: degeneration of collagen, inflammatory changes and reac-

tive necrosis¹⁰. RA is a chronic systemic inflammatory disease that can affect the skin, voluntary muscles, bones, eyes, and heart, however, the primary feature of this disease is progressive and deformative arthritis⁸ (rheumatism in which the inflammatory lesions are confined to the joints²) resulting in destruction of cartilage and bony deformities^{14, 15}. Ocular changes associated with RA include¹⁴: dry eyes, keratoconjunctivitis sicca, filamentary conjunctivitis, peripheral corneal ulceration, episcleritis and scleritis. Filamentary keratitis is best thought of as a form of aberrant corneal healing¹¹ or "keratitis with twisted filaments of mucoid material on the surface of the cornea"². Other signs of filamentary keratitis include conjunctival injection, tear film abnormalities and superficial punctuate staining¹. The most common ocular manifestation of RA is keratoconjunctivitis sicca (KCS)^{14, 16} ("a condition marked by hyperemia of the conjunctiva, lacrimal deficiency, thickening of the corneal epithelium, itching and burning of the eye, and often, reduced visual acuity"²). Common symptoms of KCS include dryness, grittiness, foreign-body sensation and burning¹⁴. Peripheral corneal furrowing can also be found in RA patients. The furrowing may start as a sclerosis of the cornea that progresses to involve the periphery of the cornea. Usually the peripheral ulceration of the cornea is sterile and is considered to be autoimmune related¹⁴.

In RA patients KCS is often caused by related Sjogren's syndrome¹⁶ (SS). Sjogren's syndrome is an autoimmune disease resulting in decreased salivary and lacrimal gland secretions, the end result of which is xerostomia and KCS respectively¹⁷. The pathophysiology of SS is considered to be a result of lymphocytic and plasma cell infiltration of the salivary and lacrimal glands¹⁷. KCS results in a compromise of the corneal surface having a direct effect on the defense mechanisms of the eye and rendering the eye more likely to develop infection. Patients with SS are not only more prone to infection but are also more at risk of developing other severe forms of ocular compromise like scleritis, corneal ulcers and nodules¹⁸. The signs and symptoms of SS include: KCS, filamentary keratitis, corneal erosions, burning, foreign-body sensation, grittiness and complaints of dry eye^{11, 16-17}.

Reactive arthritis (Reiter's syndrome): "refers

to acute nonpurulent arthritis complicating an infection elsewhere in the body. In recent years the term has been used primarily to refer to spondylarthropathies following enteric or urogenital infections... Included in this category is ...Reiter's syndrome"¹⁹. Reactive arthritis has become the term of choice for spondylarthropathies as most patients do not have the classic features of Reiter's syndrome, however, the corneal manifestations of Reiter's syndrome will be discussed here specifically¹⁹. Reiter's syndrome is characterized by a classic triad of: arthritis, urethritis and conjunctivitis²⁰. Reiter's disease often follows a venereal disease or enteric infection and very often mucocutaneous lesions occur as well^{16, 20}. The ocular manifestations of Reiter's disease are predominantly conjunctivitis (viral and bacterial) and anterior uveitis. Punctate keratitis, subepithelial infiltrates and ulcers are considered to be a more severe result of Reiter's syndrome²⁰.

Systemic lupus erythematosus (SLE): "a generalized connective tissue disorder characterized by skin eruptions, arthralgia, arthritis, anemia, pericarditis and neurologic manifestations"²². The etiology of this disease is not well understood with the pathophysiology thought to be auto-antibody production that results in immune complex deposition and tissue damage²². SLE is a multisystemic disease with manifestations including: myalgia, arthritis, myopathy, hematological disorders, nephropathy, cardiac complications, pleurisy and neuropathies^{8, 16, 22}. The corneal manifestations of SLE are predominantly KCS, superficial punctate keratitis and corneal furrowing. The presence of blood vessels close to the cornea also results in the cornea being affected indirectly by any hematological disorders that might occur. Interstitial keratitis and corneal melting have also been implicated in SLE²². Because ocular manifestations of SLE may be a marker of systemic disease it is important to detect, diagnose and refer patients with ocular findings to the relevant medical professional.

Erythema multiforme (EM): "is an acute inflammatory condition of the skin and mucous membranes that is usually self-limiting. EM can be divided into two classifications: erythema multiforme minor and erythema multiforme major (Stevens-Johnson syndrome)"²³. EM appears to be a hypersensitivity to infections and drugs and

can sometimes be idiopathic. The following conditions are associated with EM: infections (including herpes, histoplasmosis, leprosy and typhoid), drugs (sulfa-drugs, penicillins, salicylates and antimalarials) and collagen-vascular disorders (SLE)⁸. The more serious form of this disease, Stevens-Johnson syndrome, results in extensive skin and mucous membrane involvement with erosions and crusts forming around the mouth, conjunctiva, urethra and genital and perianal areas^{8,16}. The ocular aspects of EM are common with many anterior segment tissues being affected. The conjunctiva is one of the most common tissues implicated in EM. Dry eye, due to abnormality and a decrease in the number of goblet cells of the conjunctiva, is common, resulting in desiccation of the cornea. Corneal ulceration is among the more serious ocular complications of this disease²³.

Skeletal and connective tissue disease

Ehlers-Danlos syndrome: "a congenital hereditary syndrome characterized by hyperextensibility of the joints and hyperelasticity and fragility of the skin with poor healing of wounds..."². The classification of Ehler-Danlos syndrome has recently been extended to include eleven sub-types²⁴. The sub-type important to optometry is Type VI, ocular-sclerotic. Different mutations of the gene that produces type III procollagen result in the various sub-types of the disease. It appears as if the mutations result in changes to the synthesis, organization and degradation of collagen²⁵. The clinical features of the disease include: soft, hyperextensible skin, easy bruising, joint hypermobility, poor wound healing and scarring²⁵. The ocular manifestations of Ehlers-Danlos syndrome include: myopia and strabismus, epicanthal folds, retinal detachment and glaucoma. The cornea often has micro-cornea and keratoconus. The unique corneal manifestations of Type VI are keratoglobus and corneal haze²⁵. It is common for corneas or globes to rupture when exposed to minimal trauma

Nutrition

Avitaminosis A: Vitamin A is an essential nutrient for the growth and differentiation of epithelial cells found in the eye, skin, respiratory, alimentary, reproductive and uro-genital systems. It therefore plays an important role in the maintenance of

many organs found in the body¹⁶. Vitamin A plays a role in at least three metabolic processes in the eye. Firstly in the turnover and phagocytosis of the outer segments of the rods in the retina, secondly vitamin A is needed in the production of photosensitive pigments in the retina and thirdly, it is needed for the proper maintenance of the conjunctival mucosa and corneal stroma²⁶. The principal complications of avitaminosis A in the eye are related to dry eye¹⁶. Xerophthalmia and nyctalopia are leading causes of blindness and are also unequivocal indications of avitaminosis A. The World Health Organization²⁷ has categorized the ocular manifestations representing xerophthalmia into the following scheme: nyctalopia, conjunctival xerosis and Bitot's spots preceding the corneal changes of xerosis, keratomalacia or ulceration involving less than 1/3 of the cornea, keratomalacia or ulceration involving more than 1/3 of the cornea and corneal scarring. Briefly, xerophthalmia is excessive dryness of the cornea and conjunctiva resulting in the loss of luster and keratinization of the tissue.

Other hypovitaminoses that can affect the cornea are: hypovitaminosis B₁ can result in phlyctenular keratoconjunctivitis, corneal vascularization and infiltrative keratitis. Hypovitaminosis B₃ has the potential to produce epithelial erosions and hypovitaminosis B₆ and D can result in dry eyes and band keratopathy¹⁶.

Miscellaneous

Theodore's superior limbic keratoconjunctivitis usually presents as a bilateral yet asymmetrical manifestation of the following symptoms and signs: foreign body sensation, burning, photophobia and mucous discharge. The signs are: superior papillary hypertrophy, hyperemia of the superior bulbar conjunctiva and punctate epithelial erosions of the superior cornea¹³. Kunimoto *et al*²⁸ have shown that up to 50% of patients with Theodore's superior limbic keratoconjunctivitis have thyroid disease. Band keratopathy, an anterior plaque of calcium found at the level of Bowman's membrane within the palpebral aperture, can result from hyperparathyroidism, vitamin D toxicity, Paget's disease and renal failure¹. Peripheral corneal thinning can indicate systemic diseases like Wegener's granulomatosis, polyarteritis nodosa or SLE, all being manifestations of different connective tissue dis-

orders¹. Neurofibromatosis may result in corneal nerve thickening and decreased corneal sensitivity²⁹. Diabetes results in a cornea that gets injured more easily, a fact stemming from decreased sensitivity of the cornea, and takes more time to heal properly, resulting from structural changes in the basement membrane of the cornea¹⁶.

Conclusion

A variety of corneal manifestations of systemic disease have been reviewed here. Metabolic, autoimmune, nutrition and skeletal systemic disorders, among others, have been implicated in corneal disease. The list of systemic diseases covered here is not complete, however, the important aspect of this review has been to emphasize the wide variety of corneal signs that indicate the presence of systemic disease. Optometry is in a unique position in that biomicroscopy is a routine procedure in many optometric practices allowing for the detection of corneal signs that might be indicative of systemic disease. The detection, and referral, of patients with the relevant corneal signs of systemic disease is certainly something that optometrists should be aware of.

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