OCULAR MANIFESTATIONS OF AUTOIMMUNE DISEASES — Review of Literature

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SUMMARY

Objective: To increase the awareness of doctors who are treating patients with various autoimmune disorders to the fact that this group of diseases can have devastating ocular effects, especially in women and children.

Method: The available literature on autoimmune diseases, that is multi-systemic disorders that frequently affect the eyes, was reviewed. Relevant papers in journals from Pubmed and e-medicine websites were studied.

Results: Local research on autoimmune diseases and how they affect the eye is scarce, however, the journal data which was reviewed suggests that various structures of the eye could be affected. The most dreaded ocular lesion is corneal involvement. Corticosteroids and immunosupressive agents have, however, revolutionalized the management of autoimmune diseases.

Conclusion: The rheumatologist and the ophthalmologist should carry out joint management of autoimmune diseases. Prompt referral to the ophthalmologist should be done, even when there seems to be no ocular complaints; however, in many cases, ocular complications may even precede the diagnosis of autoimmune diseases.

Key words: autoimmune, ocular steroids, immunosuppressives

INTRODUCTION

Autoimmune diseases are characterized by the body's immune response being directed against its own tissues, causing prolonged inflammation and subsequent tissue destruction.[1] Any disease in which cytotoxic cells are directed against self-antigens in the body's tissue is considered autoimmune.[1]

Autoimmune diseases are characterized by HLA pathogenicity, elevated acute phase reactants, familial aggregation, female prevalence, and multi-systemic involvement. This group of diseases includes, rheumatoid arthritis, systemic lupus erythematosus, giant cell arteritis, and Sjögren's syndrome. It has been shown to respond favourably to steroids and immunosuppressive agents.[2]

Prompt diagnosis and management are necessary to prevent irredeemable ocular damage. The most serious ocular complication is corneal involvement,[3] however, the uvea, sclera, and retina may also be affected.[3]

DISCUSSION

The commonly encountered autoimmune disorders include rheumatoid arthritis, juvenile rheumatoid arthritis, systemic lupus erythematosus, Sjögren's syndrome, giant cell arteritis, Grave's disease, and in Western countries, sero-negative spondyloarthropathies and multiple sclerosis.[4] These autoimmune diseases can have devastating systemic and ocular effects. Ocular symptoms may include dry or red eyes, foreign-body sensation, pruritus, photophobia, pain, visual changes and even complete visual loss.[5] Physicians should maintain a high index of suspicion and make a timely diagnosis since a number of these diseases may present initially with ocular symptoms. A thorough ophthalmic examination including visual acuity, pupillary reaction, ocular motility, confrontation field testing, external inspection and direct ophthalmoscopy with fluorescein staining should be carried out.

In general, managing the systemic effects with nonsteroidal anti-inflammatory drugs, corticosteroids, and immunosuppressive agents also controls the ocular symptoms.[6] Surgical intervention is necessary when visual function is threatened.[6] Early and accurate diagnosis and prompt treatment or referral to an ophthalmologist may prevent ocular complications.

Most ocular complications involve the cornea, but may also affect the conjunctiva, uvea, sclera, retina and surrounding structures.[7]

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Table 1. Ocular manifestations of autoimmune diseases

Disease	Ocular manifestations
Rheumatoid arthritis	Keratoconjunctivitis sicca, scleritis, episcleritis, keratitis, ulcerative keratitis, choroiditis, retinal vasculitis episcleral nodules, retinal detachment, macular oedema
Juvenile rheumatoid arthritis	Uveitis
Systemic lupus erythematosus (SLE)	Keratoconjunctivitis sicca, conjunctivitis, uveitis, episcleritis, scleritis keratitis, retinal haemorrhages, retinal vasculitis, proliferative retinopathy, optic neuritis, ischaemic optic neuropathy, hemianopia, pupillary abnormalities, oculomotor abnormalities, visual hallucinations
Sjögren's syndrome	Keratoconjunctivitis sicca
Giant cell arteritis	Amaurosis fugax, diplopia, vision loss
Graves' disease	Proptosis/ exophthalmos, lid lag and retraction, keratitis, decreased visual acuity, reduced visual field, relative afferent pupillary defect, visual loss
Ankylosing spondylitis	Uveitis
Reiter's syndrome	Conjunctivitis, uveitis, keratitis
Enteropathic arthritis	Uveitis, episcleritis, peripheral ulcerative keratitis
Psoriatic arthritis	Uveitis, conjunctivitis, keratitis
Multiple sclerosis	Afferent: optic neuritis, retrobulbar neuritis, visual field defects Efferent: internuclear ophthalmoplegia, dysmetria, nystagmus, cranial nerve palsies
Myasthenia gravis	Diplopia, eyelid ptosis
Sarcoidosis	Uveitis, conjunctival nodules, cranial nerve palsies, enlarged lacrimal gland, optic neuropathy
Wegener's granulomatosis	Proptosis/exophthalmos, orbital cellulitis, uveitis, corneal ulcers, optic neuropathy
Behçet's syndrome	Uveitis, hypopyon
Antiphospholipid syndrome	Vaso-occlusive retinopthy, ischaemic optic neuropathy
Polyarteritis nodosa	Episcleritis, optic neuropathy
Takayasu arteritis	Vaso-occlusive retinopathy, ischaemic optic neuropathy, cataracts
Dermatomyositis	Eyelid/conjunctival oedema, retinopathy, uveitis

Rheumatoid arthritis (RA)

Ocular manifestations occur in approximately 25% of patients with rheumatoid arthritis.[8] These may include keratoconjuctivitis sicca, scleritis, episcleritis, keratitis, peripheral corneal ulceration, and less commonly, choroiditis, retinal vasculitis, episcleral nodules, retinal detachments and macular oedema.

Keratoconjuctivitis sicca or dry eye syndrome. This is the most common ocular manifestation of RA and has a prevalence of 15 - 25%.[9] Symptoms are more prominent during the later part of the day because of the evaporation of the tear film.[10] Schirmer's test is valuable in assessing the function of the lacrimal glands. This is performed by first drying the tear film, then inserting a Schirmer strip into the lower conjunctival cul-de-sac towards the temporal aspect of the lower lid. No anaesthetic should be used. After five minutes, if the strip measures less than 10 mm of wetting, the lacrimal glands are not functioning properly.[11] A corneal examination with a slit lamp may reveal a punctate erosive keratopathy or filaments.[12]

The primary goal in managing dry eye is to replenish or preserve the tear film. Educating the patient about simple measures such as using sunglasses and room humidifiers and avoiding dry environments is very important.[13] Natural or artificial tear substitutes can help alleviate severe symptoms but many contain preservatives that can be toxic to the cornea.[13] Surgical tarsorrhaphy may be necessary in severe cases.[13]

Scleritis or episcleritis. Patients with RA have a prevalence rate of 4-10% for scleritis or episcleritis.[5] Rheumatoid arthritis is the most common cause of scleritis, accounting for approximately 18 to 33% of cases.[5] Scleritis and episcleritis are distinguished on the basis of anatomy and appearance.[14] Symptoms may be similar, but the pain in scleritis is more severe. Patients with scleritis experience tenderness on global palpation, while those with episcleritis do not.[14] Scleritis should be diagnosed as distinct from episcleritis because of the potential ocular complications of scleritis.[15] Patients with scleritis also have more widespread systemic disease and a higher mortality rate than those without scleritis.[15]

The instillation of one to two drops of 2.5% of topical phenylephrine (neo-synephrine) can help distinguish dilated vessels caused by scleritis from those caused by episcleritis; the eye drops in the affected eye will cause the engorged vessels of episcleritis to blanch, while those of scleritis remain dilated.[16] This test should, however, not be done in patients with a history of glaucoma.[16]

There are two types of scleritis: necrotizing scleritis with inflammation and non-necrotizing scleritis. Necrotizing scleritis is the more destructive.[17] In addition to the ocular findings in non-necrotizing scleritis, avascular areas of the sclera or necrosis may be seen, with surrounding scleral oedema. Scleral thinning, staphyloma, or perforation may complicate this. Necrotizing scleritis without inflammation is a sign of long standing RA and can lead to scleromalacia perforans.[17]

Table 2. Ocular symptoms, sign and treatment of autoimmune diseases

Condition	Symptoms	Sign	Treatment
Keratis	• Pain with photophobia • Foreign body sensation • Tearing, red eye • Decreased vision	• Inflammatory cell infiltrate • Corneal opacification • Corneal vascularization • Corneal ulceration	• NSAID • Topical oral/IV steroids • Immunosuppressives • Surgery
Keratoconjuctivitis sicca	• Dry eye, burning • Pain, blurred vision • Pruritus • Foreign body sensation • Mucous threads • Crusting about the eyelids	• Diminished corneal tear meniscus • Abnormal Schirmer's test	• Sunglasses • Room humidifier • Tear substitutes • Surgery
Scleritis	• Gradual onset • Deep boring pain, pain may radiate into cheek, eyebrows and temples • Blurred vision • Photophobia	• Decreased visual acuity • Engorged blood vessels • Immovable tender nodules over the sclera • Tenderness on palpation	• NSAID/ topical / oral/IV steriods • Immunosuppressives • Surgery
Episcleritis	• Sudden onset • Mild ache, may radiate into cheek, eyebrows and temples • No blurred vision • Photophobia	• No change in visual acuity • Engorged blood vessels • Immovable, tender nodules over the sclera • Tenderness on palpation	• NSAID • Topical / oral steriods • Immunosuppressives • Surgery
Uveitis	• Red eye • Pain • Photophobia • Blurred vision	• Decrease in visual acuity • Inflammatory infiltrate in the anterior chamber • Synaechae • Pupillary miosis	• Cycloplegics • Topical steriods • Immunosuppresives
Optic neuritis	• Visual loss • Pain with eye movement • Photophobia	• Decreased visual acuity • Loss of colour vision • Central scotoma • Afferent pupillary defect • Swollen optic nerve	• IV steriods (with positive MRI findings)
Exophthalmos	• Irritable and gritty eyes • Blurred or double vision • Photophobia • Increased tearing • Orbital pressure	• Protruding globe • Widening palpebral fissures • Conjunctival injection and chemosis • Lid lag and retraction • Extraction keratitis	• Lubricating eye drops • Sleeping with head elevated • Sunglasses • Eyelids taping at night • Steriod • Radiotherapy • Surgery

The two types of episcleritis are simple episcleritis and nodular episcleritis. The distinguishing feature is the presence of subconjunctival nodules that are mobile over the sclera in nodular episcleritis.[18] Simple episcleritis is more common in RA.[18]

The initial treatment of scleritis and episcleritis should focus on relieving discomfort and stopping the progression of the disease.[19] The initial therapy includes the use of non-steroidal anti-inflammatory drugs.[19] Non-responders should be referred to an ophthalmologist.

Corneal disease. In patients with RA, corneal disease may be an isolated complication, but it is commonly associated with keratoconjuctivitis sicca or anterior scleritis.[20] Corneal disease may include keratitis, sclerosing keratitis, and peripheral ulcerative keratitis.[20] Keratitis associated with scleritis may be acute or sclerosing. Acute keratitis has been identified in 30-70% of patients with scleritis associated RA.[20] There is an intense inflammatory cell infiltrate that may result in cornea scarring, ulceration or melting.

Sclerosing keratitis is a chronic process marked by an area of opacified and vascularized cornea that progresses toward the visual axis. Without treatment, perforation and visual loss may occur.[21] In order to preserve vision, the application of a topical steroid, immunosuppressive therapy, surgical intervention, or a combination of the above, will be required.[22] Surgical options include ulcer debridement, conjunctival resection, corneal graft, application of tissue adhesives, sclerectomy, and scleral patch grafting.[22]

Other less common ocular manifestations of RA include choroiditis, retinal vasculitis, episcleral nodules, exudative or serous retinal detachments, and macular oedema.[23] A high index of suspicion can preserve vision and prevent further ocular complications.

Juvenile rheumatoid arthritis (JRA)

Approximately 80% of cases of uveitis in children are due to juvenile rheumatoid arthritis (JVR).[24] A particular subtype of JVR is responsible for the majority of the cases of uveitis, although uveitis can be found in all forms of JVR.[24] Most patients will be symptom free or have blurred vision. Delayed diagnosis can lead to cataracts, glaucoma, and blindness.[24] Ocular examination may reveal decreased visual acuity, band keratopathy, synechiae, cataract or elevated ocular pressure. Prompt referral to an ophthalmologist is indicated.[25] Therapies involve the use of cycloplegic agents, steroids, NSAIDS or immunosuppressive agents.[25]

Table 3. Juvenile rheumatoid arthritis risk categories for developing uveitis and recommended ocular examinations

Risk	Recommendations
High: should have ocular examination every 3 months	• Pauci or polyarticular arthritis; • Positive for anti-nuclear antibodies • Onset of arthritis <= 7 yrs • Duration of arthritis <= 4 yrs
Moderate: should have ocular examination every 6 months	• Pauci or polyarticular arthritis • Positive for anti-nuclear antibodies • Onset of arthritis <= 7 yrs • Duration of arthritis <= 4 yrs
Low: should have ocular examination every 12 months	• Pauci or polyarticular or systemic arthritic • Negative for anti-nuclear antibodies • Onset of arthritis <= 7 yrs • Duration of arthritis <= 4 yrs

Systemic lupus erythematosus (SLE)

About 20% of patients with SLE will develop an ocular disease.[26] The ocular disease may precede or follow systemic manifestations of SLE or may indicate reactivation of SLE that was thought to be in remission.[26]

External ocular manifestations include keratoconjuctivitis sicca, which is the most common symptom. Others include conjunctivitis, uveitis, episcleritis, scleritis, keratitis, and a discoid lupus rash over the eyelids.[27] Microinfarction, haemorrhage, or vasculitis may be responsible for neuro-ophthalmic involvement in SLE.[28] The complications include optic neuritis, ischaemic optic neuropathy, hemianopia, amaurosis, internuclear ophthalmoplegia, pupillary abnormalities, oculomotor abnormalities, pseudotumour cerebri and visual hallucinations.[28]

Retinal disease primarily occurs in patients with active SLE and may include cotton-wool spots, retinal haemorrhages, retinal vasculitis, or proliferative retinopathy.[29] Treatment of retinal diseases is based on the specific pathology and underlying disease.[29] Aggressive treatment by an ophthalmologist should be carried out because of its high morbidity.[29]

Most physicians agree that patients on antimalaria or steroid regimens should receive a full dilated-eye examination on initiation of therapy, routine examination in low-risk patients and yearly examination for high-risk patients.[30] High risk is defined as medication dosage (>6.5 mg per kg hydroxychloroquine or > 3 mg/kg chloroquine), duration of use (more than 5 years), high body fat level, presence of renal or liver disease, presence of concomitant retinal disease, and age greater than 60 years.[30]

Sjögren's syndrome

The primary ocular manifestation of Sjögren's syndrome is keratoconjunctivitis sicca.[31] The symptoms are similar to keratoconjunctivitis sicca associated with RA.[31] The lacrimal gland is the main contributor to the aqueous layer of the tear film.[32] It secretes proteins, electrolytes and water, which help to nourish and protect the ocular surface.[32] The secretion of lacrimal fluid is activated by both the efferent parasympathetic and sympathetic nerves in the lacrimal gland. A decrease or lack of lacrimal gland secretion is the leading cause of aqueous tear-deficient dry eye syndrome (DES).[33] The lacrimal gland is a target of the immune system in several pathological instances, and it will show signs of inflammation. The hallmarks of lacrimal gland inflammation are the presence of focal lymphocytic infiltrates and an increased production of pro-inflammatory cytokines.[34] The mechanisms leading to lacrimal gland dysfunction are still poorly understood. Apoptosis, the production of autoantibodies, hormonal imbalance, alteration in signaling molecules, neural dysfunction, and increased level of pro-inflammatory cytokines have been proposed as possible mediators of lacrimal gland insufficiency in Sjögren's syndrome.[35] The patient usually complains of dry eyes, including burning, itching, or foreign body (gritty, sand) sensation and the accumulation of thick, ropy secretions along the inner canthus of the eyes.[36] With time, conjunctiva injection, reduced visual acuity and increased photosensitivity develop. These symptoms, which occur because of the decreased and altered tear production, result in the destruction of the corneal and bulbar conjunctiva epithelium defined as keratoconjunctivitis sicca.[37] Oral pilocarpine (Salagen) 5 mg, four times a day, may improve the symptoms of dry eyes and dry mouth.[38] Diaphoresis and poor night vision are the attendant side effects.[38]

Giant cell arteritis

Ocular symptoms occur in about 50% of patients with giant cell arteritis.[39] The ocular symptoms include pain, diplopia, visual loss, and amaurosis fugax, in addition to headache, jaw claudication, and neck pain.[39] Ocular

involvement is common in the absence of systemic signs and symptoms.[39] Patients may have temporal artery tenderness or a decreased temporal artery pulse. Diagnosis is confirmed with temporal artery biopsy and elevated erythrocyte sedimentation rate and C-reactive protein.[39] Biopsy may remain positive for two weeks after the initiation of corticosteroid therapy.[40] A high dose of corticosteroid is usually indicated and response is usually dramatic.[40]

Graves' disease

Eye signs noted in patients with thyrotoxicosis include stare, lid lag, lid retraction exophthalmos and conjunctival injection or oedema. These symptoms are accompanied by orbital pain, lacrimation, irritation and photophobia.[41] These eye signs are largely due to excessive adrenergic stimulation and they remit promptly upon successful treatment of thyrotoxicosis.[42]

Infiltrative ophthalmopathy is a more serious development and is specific for Graves' disease.[42] It results in a spectrum of ocular muscle weakness frequently leading to blurred and double vision.[42] Computed tomography or magnetic resonance imaging of the orbit is recommended if there are signs of optic nerve compression, such as decreased visual acuity, reduced visual fields, relative afferent pupillary defect, and loss of colour vision.[42]

The pathogenesis of infiltrative ophthalmopathy is poorly understood.[42] It may occur before the onset of hyperthyroidism, or as late as 15 to 20 years afterward and frequently worsens or improves independent of the clinical course of hyperthyroidism.[42] Infiltrative ophthalmopathy results from immunoglobulins directed to the extraocular muscles.[42] Typical ophthalmopathy in the presence of normal thyroid function is known as euthyroid Grave's disease[42]

Patients suspected to have infiltrative ophthalmopathy disease should be referred to an ophthalmologist for full-dilated ocular examination. Mild infiltrative ophthalmopathy can be treated with simple methods such as lubrication drops applied hourly, sleeping with the head elevated, wearing sunglasses during the day, and taping eyelids closed at night.[43] Systemic corticosteroid therapy or radiotherapy is reserved for more severe cases and surgical decompression of the orbit or tarsorrhaphy may be required in patients with sudden visual loss or extensive corneal damage respectively.[43]

Spondyloarthropathies

Uveitis is the commonest ocular presentation of the seronegative spondyloarthropathies.[45] It occurs in approximately 25% of patients with ankylosing spondylitis; in 37% of patients with Reiter's syndrome; in 30 % of patients with psoriatic arthritis; and in up to 9% of patients with enteropathic arthritis (arthritis associated with Crohn's disease or ulcerative colitis).[45] Ocular symptoms can be unilateral or bilateral and pain is caused by a ciliary spasm in response to anterior chamber inflammation.[45] Complications include glaucoma, cataracts and blindness.[45]

Multiple sclerosis (MS)

The ocular manifestations of multiple sclerosis can be divided into afferent and efferent disease.[46] Optic neuritis is the first presenting symptom in 14 - 25% of patients; another 75% of the patients with multiple sclerosis eventually present with optic neuritis.[46] Demyelination is responsible for visual field defects and bilateral internuclear ophthalmoplegia.[47] Brain stem and cerebellum lesions may present as dysmetria, nystagmus and cranial nerve palsies, especially of the third and sixth nerves.[47]

Nystagmus, which may be the first neurologic finding in patients with MS, is commonly horizontal but may also be rotary or vertical.[48] Magnetic resonance imaging is indicated and if positive, intravenous corticosteroid should be instituted.[49] Periodic follow-up evaluations should be done to monitor disease progression.

Behçet's disease

Ocular complications occur in 50-70% of affected patients. The most common is a relapsing iridocyclitis, sometimes with hypopyon, that often presents as pain, photophobia, and hazy vision.[50] The posterior segment may also be involved, with choroiditis, retinal vasculitis, and papillitis.[51] Untreated posterior uveitis may cause blindness.[51] Other presentations include blurred vision, periorbital pain, scleral injection and excessive lacrimation. Fluorescein angiography may show leaky retinal vessels. Atrophy and fibrosis may be the ultimate outcome.[52]

Wegener's granulomatosis

Ocular manifestations include nasolacrimal duct obstruction, retrobublar granuloma with proptosis, episcleritis, uveitis and optic neuritis.[53]

Dermatomyositis

A deep violet red rash may be present on the face, particularly in the periorbital areas, which may also be oedematous. Involvement is most prominent over the upper eyelids, and scaling may also occur here.[54] Lilac suffusion or heliotrope rash over the upper eyelids is a characteristic of dermatomyositis.[55] Ocular myopathy (muscle wasting) can occur in a small proportion of patients leading to double vision; a few people develop retinopathy.[56]

Antiphospholipid syndrome (APS)

Retinal vaso-occlusive disease and optic neuritis are well-recognized manifestations of APS. Transient partial

or complete visual loss, diplopia, and field defects have been reported.[57] These defects may be monocular or binocular.

Myasthenia gravis

Presentations include ptosis, diplopia, and blurred vision. Ptosis and diplopia are by far the most common complaints.[58] Findings may not be apparent unless muscle weakness is provoked by repetitive or sustained use of the muscles involved.[59,60]

Polyarteritis nodosa (PAN)

The ocular manifestations of PAN include retinal vasculitis, retinal detachment, and cotton-wool spots.[61,62] All patients with systemic PAN should therefore be screened and have an ophthalmologic examination.

Sarcoidosis

Anterior uveitis is the most common finding with sarcoidosis. It may be associated with fever and parotid swelling (also called uveoparotid fever).[63] Chronic uveitis, which commonly occurs in African Americans, can lead to adhesion, glaucoma, cataract formation, and blindness.[64] Although uveitis is most common, any part of the eye may be affected.[65]

Takayasu arteritis

The symptoms which may indicate takayasu arteritis during an ophthalmologic examination are retinal haemorrhages, cotton-wool exudates, venous dilatation and beading, microaneurysms of the peripheral retinal, optic atrophy, vitreous haemorrhage, and classic wreath-like peripapillary arteriovenous anastomosis.[66] There may be transient or permanent blindness.[67]

Systemic sclerosis

The most common complaint is dryness in the eyes. A minority of patients may develop retinopathy with cotton-wool spots at the back of the eyeball, retinal hemorrhages and occlusion of retinal arteries.[68]

SUMMARY

Autoimmune diseases run the gamut, from mild to disabling and potentially life-threatening. Nearly all affect women more frequently than men. The question before the scientific community is 'why?'. We have come a long way in the diagnosis and treatment of autoimmune diseases. More work is, however, needed, especially in the areas of discovering the causes and developing more effective treatment and prevention strategies.

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