Epidemiology and pathogenesis of uveitis: A review

Jyotirmay Biswas

Director, Uveitis & Ocular Pathology Department, Sankara Nethralaya, Chennai, Tamil Nadu, India

Abstract

Uveitis is a complex multifactorial autoimmune disease. The four anatomical types of uveitis include anterior uveitis, intermediate uveitis, posterior uveitis and panuveitis. Most of the uveitic entities are idiopathic. The disease is more common in males with mean age group of 35 to 45 years. Advanced diagnostic tests like molecular biologic study of intraocular fluid in infectious uveitis and high-resolution CT chest imaging techniques have contributed to etiological diagnosis of uveitis. The disease can cause varying degrees of visual loss. In the US, uveitis has been identified as a cause for 10% of the legal blindness. Although exact visual morbidity due to uveitis in India is unknown, it appears to be relatively more when compared to developed countries. HLA-B27 anterior uveitis accounts for 50% of acute anterior uveitis. Intermediate uveitis is mostly idiopathic. Posterior uveitis can be infectious or non-infectious. Infective uveitis is more common in developing countries like India. Visual loss is more common in panuveitis. Pathogenesis of uveitis varies according to the disease entity. This review article describes the epidemiology and pathogenesis of the major uveitic entities.

Introduction

The word uvea, originated from the Latin word ‘uva’, means grape. Uvea comprises of iris, ciliary body and choroid. Inflammation of the uveal tract is called uveitis. Standardisation of Uveitis Nomenclature (SUN) has divided uveitis into four anatomical types, anterior, intermediate, posterior and panuveitis. Uveitides are a collection of about 30 diseases. Anterior uveitis, earlier known as iritis or iridocyclitis, affects the anterior part of the uvea and is the commonest form of uveitis. It is generally treated with eye drops. Intermediate uveitis affects the middle layer of the uveal tract. It is generally treated with tablets and periocular or intraocular injections. Posterior uveitis affects retina and/or choroid. It can be retinitis, choroiditis, retinochoroiditis and chorioretinitis. It is usually treated with systemic medications than drops. Panuveitis is the term used for inflammation affecting the entire uveal tract. Uveitis, can be caused by infections like tuberculosis, toxoplasmosis and syphilis. It can be associated with systemic diseases like sarcoidosis and Behcet’s disease. Rothova et al have noted a definite association of systemic disease in 25% of the cases with uveitis. In developing countries like India, infectious uveitis accounts for up to 50% of the cases. The cause of uveitis is often undetermined and many of them are of autoimmune etiology.

Epidemiology of uveitis

The average annual incidence of uveitis has been reported to be around 14-17 per 100,000. The total population prevalence of uveitis varies geographically and has been roughly estimated to be around 38 per 100,000 in France, 200 per 100,000 in the US, and 730 per 100,000 in India. For an estimated population of 1168 million in 2010, the prevalence rate of uveitis in India was around 8.5 million. The incidence of new cases noted in a tertiary care ophthalmic center in India was 1.5%. Various clinic-based surveys indicate that 60 to 80% of patients with uveitis belong to third to sixth decade of life with a mean age of presentation between 35 and 45 years. The estimated prevalences of uveitis in children and elderly were 5 -16% and 6-21% respectively. Most uveitic surveys indicate an equal gender distribution. However, reports from India indicate a male preponderance. An Indian study has reported that 62% of the affected subjects were males.
and 38% were females. The same study has found that anterior uveitis was the most common anatomical type (40%), followed by posterior uveitis (29%), intermediate uveitis (17%) and panuveitis (14%). In a study in 1996, the etiology was undetermined in 59.31% of the cases. But a recent study from North India and an unpublished study by the author has reported it be around 40%. Diagnostic modalities like polymerase chain reaction of intraocular fluid in infectious uveitis and radiologic modalities like high resolution computerized tomography of the chest have improved the etiological diagnosis of uveitis. Anterior uveitis and intermediate uveitis are often idiopathic. The common cause of posterior uveitis is tuberculosis and panuveitis is Vogt-Koyanagi-Harada disease. Several uveitic diseases like birdshot chorioretinopathy, presumed ocular histoplasmosis syndrome and Lyme disease are not seen in India.

Uveitis, the fifth commonest cause of visual loss in the developed world, can cause varying degrees of visual loss. In the US, the disease accounts for 10% of the legal blindness. Visual morbidity due to uveitis was not evaluated in India. But experts feel that it will be higher than the developed countries.

**Anterior uveitis**

Anterior uveitis, the inflammation of the iris, can be nongranulomatous or granulomatous (Fig. 1). About 30% of acute anterior uveitis is non-infective and is associated with HLA-B27 haplotype. This type of uveitis is typically nongranulomatous. These patients often have reactive arthritis, ankylosing spondylitis, inflammatory bowel disease and psoriatic arthritis. A retrospective study involving 42 patients with anterior uveitis at a tertiary care eye hospital in south India has found that 33.3% were HLA-B27 positive. Three of them had juvenile idiopathic arthritis, two ankylosing spondylitis, two had systemic tuberculosis, two had systemic sarcoidosis and one with Vogt-Koyanagi-Harada disease. Exact pathogenesis of HLA-B27 positive anterior uveitis is unknown. Gram-negative bacilli in the gut or chlamydia infection might play a role. Recent research indicates the possibility of gut microbiome in causing HLA-B27-related uveitis. The study on experimental autoimmune uveitis (EAU) by Rosenbaum et al. in mice models has shown that oral antibiotics modulate the severity of EAU by increasing lymphocytes in the gut and extra-intestinal tissues and by decreasing effectors T cells and cytokines. The study suggests that protective and uveitogenic bacteria exist and some antibiotics may be able to alter the microbiota away from the uveal tissue. Whereas, other antibiotics may promote potentially uveitogenic bacteria. Such findings indicate the importance of gut microbiome in autoimmune uveitis. This can be a potential target for therapeutic intervention.

The common causes for granulomatous uveitis include tuberculosis, sarcoidosis, and leprosy. Tuberculous anterior uveitis often has mutton-fat keratic precipitates, broad posterior synechiae and iris nodules. In most cases, testing of aqueous aspirate for acid fast bacilli and culture for mycobacterium tuberculosis are negative. However, polymerase chain reaction of aqueous aspirate for mycobacterial DNA is often positive. Nowadays, anterior chamber paracentesis with polymerase chain reaction of aqueous aspirate is conducted in many centers in India to establish or rule out tubercular etiology. Anterior uveitis due to sarcoidosis often mimics tubercular uveitis. Elevated serum angiotensin converting enzyme, elevated
lysozyme level, negative tuberculin test and characteristic hilar lymphadenopathy on chest X-ray or computerized tomography of the chest help in distinguishing sarcoidosis from tuberculosis.

**Intermediate uveitis**
Inflammation of the ciliary body and vitreous is termed as intermediate uveitis and the disease is often idiopathic (Fig. 2). The disease occurs in children as well as young adults. The most common symptoms are floaters and blurring of vision. Common identifiable causes of intermediate uveitis are sarcoidosis and tuberculosis. Rare causes of intermediate uveitis are multiple sclerosis and Lyme disease.

**Posterior uveitis**
Inflammation of the retina and choroid is called posterior uveitis (Fig. 3). About one third of uveitis is posterior uveitis. It can be non-infective or infective. Causes for non-infective posterior uveitis are acute posterior multifocal placoid pigment epitheliopathy (APMPPE), sarcoid posterior uveitis, birdshot retinochoroidopathy, and serpiginous choroiditis. Posterior uveitis can also be caused due to several infectious agents like protozoa (Toxoplasma), helminth (Toxocara), bacteria (mycobacterium tuberculosis), and treponema (syphilis). Serpiginous choroiditis, especially multifocal type, was earlier thought to be of autoimmune etiology. Recent research has identified the cause as latent infection of mycobacterium tuberculosis. Most of the patients with posterior uveitis have metamorphopsia and distortion of central vision, if macula is involved.

**Panuveitis**
Inflammation of entire uveal tract is called panuveitis (Fig. 4). The disease can be due to autoimmune etiology like Vogt-Koyanagi-Harada disease, sympathetic ophthalmia,
and Behcet’s disease. Infective etiologies include mycobacterium tuberculosis, and syphilis. Among all uveitic entities, panuveitis causes gross reduction of vision.

Pathogenesis of specific uveitic entities are given below.

**HLA-B27-positive acute anterior uveitis**
Acute anterior uveitis (AAU) is a common form of anterior uveitis. The symptoms include pain, redness, photophobia and diminution of vision. Slit lamp examination reveals circumciliary congestion, fine keratic precipitates, marked aqueous flare and sometimes fibrin or hypopyon. Intraocular pressure is often reduced, and anterior vitreous cells and macular edema might be present. Around 50% of patients with acute anterior uveitis is HLA-B27 positive. There is increasing evidence that genes other than HLA-B27 influence the risk of developing AAU. Studies conducted in animal models suggest the role of innate immunity, the IL-23 cytokine pathway and exogenous factors in the pathogenesis of AAU. The association with some gram-negative bacteria and chlamydia has been established. However, the use of systemic antibiotic has not been found to be beneficial.

**Collagen diseases**
Collagen diseases that can cause uveitis and scleritis include rheumatoid arthritis, granulomatous polyangiitis (Wegener’s granulomatosis), and systemic lupus erythematosus (SLE). Scleritis is more common in rheumatoid arthritis and granulomatous polyangiitis. SLE is a multisystem autoimmune disease with ocular involvement in one third of the cases. Annual incidence of SLE varies from 0.3 to 8.7 per 100,000 per year and prevalence from 1.1 to 534.9 per 100,000. SLE rarely causes anterior uveitis, but it causes more retinal pathology. Lupus retinopathy occurs in 10% of the patients. The disease is often bilateral, presenting with retinal hemorrhages, cotton wool spots, arteriolar narrowing with capillary and venous dilation, and vascular tortuosity. Retinal edema, exudates and microaneurysms are often noted. The disease is considered as an immune complex vasculopathy with fibrinoid degeneration.

**Sarcoid uveitis**
Sarcoidosis, a chronic multisystem granulomatous disease with non-caseating epithelioid cell granuloma, may affect any organ system. Ocular involvement is seen in 83% of the patients and can be the presenting sign. Six clinical findings, viz. iris, and anterior chamber angle nodules, mutton-fat keratic precipitates, chorioretinal granuloma, vitreous string of pearls, snowball exudates, retinal perivasculitis and candle wax drippings, indicate ocular sarcoidosis.

Hilar lymphadenopathy on chest X-ray or high-resolution CT chest and elevated serum angiotensin converting enzyme assist in disease diagnosis. Histopathology of transbronchial biopsy shows lymphocytosis with increased CD4 and CD8 lymphocytes. The disease is mediated by abnormalities in cell-mediated and humoral immunity. These lead to impaired responsiveness to antigen recognition, reduced circulating T cell levels, elevated globulin levels and non-specific elevation of antibody titers. Sarcoid uveitis is treated with topical and systemic steroid. Non-responsive cases can be treated with various

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Fig. 4: Fundus photograph of a case of panuveitis due to Behcet’s disease showing vitreous haze and retinal vasculitis with exudates
immunosuppressive drugs.

**Serpiginous and multifocal serpiginoid choroiditis**

Serpiginous choroiditis starts from the juxtapapillary choroid and spreads centrifugally. Margins are wavy. This type of choroiditis involves overlying retinal pigment epithelium and the outer retina. The disease occurs in middle aged, otherwise healthy individuals. There is no familial or ethnic predilection. An Indian study conducted at a uveitis referral center has noted serpiginous choroiditis in 18.9% of the cases. Multifocal serpiginoid choroiditis occurs in relatively younger individuals. There is often overlying vitritis. This type of choroiditis is seen more commonly in tuberculosis endemic regions. They are often positive for Mantoux and quantiFERON TB gold tests. Chest X-ray or high-resolution CT chest often shows features of active or latent TB. Mycobacterial tuberculosis DNA is commonly noted in aqueous or vitreous samples. The disease often causes damage to the photoreceptors, and the involvement of fovea causes irreversible visual loss. The disease is a common posterior uveitis in India. An Indian study has reported the prevalence to be 10.9% of all posterior uveitis cases.

An autoimmune etiology is suspected, but specific trigger for such localized immune response is not known. A higher frequency of HLA-B7, HLA-A2, HLA-B-8 and HLA-Dw 3 has been noted in serpiginous choroiditis patients, in contrast to the general population, thereby indicating a possibility for genetic predisposition. Serpiginous choroiditis also shows autoreactivity of circulating lymphocytes to retinal S antigen. Detection of mycobacterial DNA in the aqueous or vitreous indicates that such DNA can trigger immunologic response. There is also possibility of molecular mimicry causing such immune reaction. The disease often responds to corticosteroids and immunosuppressive agents. Antitubercular therapy is sometimes combined with corticosteroids to prevent the recurrences.

**Vogt-Koyanagi-Harada disease**

Vogt-Koyanagi-Harada disease is typically a bilateral panuveitis associated with neurologic features like meningismus and dysacusis in acute stage, and dermatological manifestations like vitiligo, alopecia and poliosis in chronic phase. Patients often have bilateral serous retinal detachment in acute stage and sunset glow fundus in the chronic stage. The disease occurs in pigmented races like Asians, Hispanics and Native Americans. The disease occurs most often in second to fifth decades of life. In India, the disease prevalence is around 21% of those affected with panuveitis. It has been found to be associated with certain HLA genotypes (DRB1 *0405). The disease is thought to be caused by an autoimmune reaction to melanocytes or to tyrosinase-related peptides.

Pathology reveals a granulomatous inflammation of the uveal tract. There is diffuse infiltration of lymphocytes, macrophages and epithelioid cells. Dalen-Fuchs nodules are sometimes seen between retinal pigment epithelium and Bruch’s membrane as collection of lymphocytes and epithelioid cells. Immunohistochemical study of ocular tissue has shown predominant infiltration of T lymphocytes. Class II major histocompatibility antigens are expressed in choroidal melanocytes and in the endothelium of the choriocapillaries. The disease in acute stage is treated with intravenous methyl prednisolone or high dose of oral prednisolone. Immunosuppressive agents are used in refractory cases and in chronic phase.

**Sympathetic ophthalmia**

It is a rare disease with unique presentation, occurring in 0.03 per 100,000 population. The disease manifests as bilateral panuveitis due to penetrating injury or surgical trauma to one eye leading to panuveitis in both the eyes. The disease occurs usually after 2 weeks of penetrating injury or surgery. In around 65% of the cases, it occurs within two months and in 90% within one year after trauma or surgery. There is often granulomatous uveitis with exudative retinal detachment and yellow white spots corresponding to Dalen-Fuchs nodules. Optic disc involvement (papillitis) is common. The disease has been noted in about 0.01% of patients who had undergone parsplana vitrectomy. The exact cause of sympathetic ophthalmia is unknown. The disease was found to be associated with HLA- A1 in 32% of the subjects. In Japanese patients, HLA DR4 and DRW 53 were found to be associated with sympathetic ophthalmia.

Histopathological finding shows a diffuse thickening of the choroid due to infiltration of chronic inflammatory cells consisting predominantly of lymphocytes along with focal collections of epithelioid cells and occasional giant cells. On immunophenotyping, the lymphocytes are found to be predominantly T-lymphocytes with a small number of B-cells (initially predominated by CD4+ and later by CD8+ cells). The choroid shows marked thickening, but the
Choriocapillaris are relatively spared. Nodular clusters of epithelioid cells are seen between the RPE and Bruch's membrane and these clusters are known as Dalen-Fuch's nodules. These nodules express HLA-Class II antigens on their surface and may be involved in presenting ocular antigen to the T-cells. The antigen leading to sympathetic ophthalmia is unknown. It may be S antigen or interphotoreceptor retinoid binding protein (IRBP) released by trauma, which subsequently incites an autoimmune reaction. Since perforating trauma and uveal incarceration are seemed to be etiologically important, the organisms entering the eye at the time of injury might be acting as adjuvants, with the conjunctival lymphatics carrying these uveal and bacterial antigens into the circulation.

**Behcet's disease**

It is a chronic relapsing vasculitis that may affect almost all the organs. The disease is characterized by four major symptoms: ocular (panuveitis and occlusive vasculitis), aphthous ulcers, genital ulcers, and dermatological lesions (erythema nodosum and subcutaneous thrombophlebitis). If all the four major symptoms are present, the disorder is called complete Behcet's syndrome. If only three of the four features are seen, it is labeled as incomplete Behcet's syndrome.

The underlying pathology for all Behcet's lesions is occlusive vasculitis with marked perivascular infiltration of lymphocytes and mononuclear cells. Endothelial cell proliferation is also present and together these lead to the occlusion of small blood vessels. Retinal examination shows atrophy of the nerve fiber layer and necrosis of other superficial retinal layers.

The disease has a marked predilection of HLA-B51. Out of the three alleles of HLA B51 antigen, HLA B*5101, HLA B*5102 and HLAB*5103, only HLA B*5101 has been found to be associated with Behcet's disease. Although the exact antigen has not been identified, various hypotheses are postulated. These patients show enhanced cell-mediated cytotoxicity for oral epithelial cells. The skin and aphthous lesions show streptococcal antigen in vitro. Immune complex-mediated damage has also been proposed, but the nature of the antigen in these complexes is unknown.

An immunopathologic study of an eye, removed at autopsy from a patient with active Behcet's disease, showed intramural and perivascular infiltration of lymphocytes, which stained positively for CD4 and IL-2 receptor surface markers. A few cells in the optic nerve head, retinal vascular endothelium and retinal pigment epithelium were HLA-DR positive. These studies indicated the possible role of cell-mediated immunity in tissue damage in Behcet's disease. The disease is treated with immunosuppressive agents like azathioprine and cyclosporine. Recently, biologic agents have been found to be beneficial in the management of ocular Behcet's disease.

**White dot syndromes**

These are group of disorders presenting as multiple whitish yellow inflammatory lesions, located at the level of outer retina, retinal pigment epithelium and choroid. These include acute posterior multifocal placoid pigment epitheliopathy (APMPPE), birdshot chorioretinopathy, diffuse unilateral subacute neuroretinitis (DUSN), multiple evanescent white dot syndrome (MEWDS), multifocal choroiditis with panuveitis (MFC), acute zonal occult outer retinopathy (AZOOR) and serpiginous choroiditis. The etiology of the white dot syndromes is not completely understood. Various mechanisms of disease have been postulated. These include infectious and non-infectious causes.

**Retinal vasculitis**

Retinal vasculitis is a relatively rare group of diseases characterized by inflammation of retinal blood vessels. There is often associated uveitis. The incidence in the US is estimated to be 1-2 new cases per 100,000 population annually. Retinal vasculitis has characteristic sheathing of retinal blood vessels, vascular leakage, vascular occlusion, cotton wool spots, intra-retinal hemorrhage and are often associated with intraocular inflammation. In a study from eastern India, involving 113 eyes of 70 patients with retinal vasculitis, 85.7% were males and 14.3% were females. Vasculitis was bilateral in 61.47% and unilateral in 38.6% patients. Commonest symptoms were dimness of vision (64.6%) and floaters (31.9%). Vascular sheathing (72.6%) and vitritis were the most commonly reported signs. None of the 70 patients had systemic diseases. Eales' disease is the most common retinal vasculitis noted in the Indian subcontinent. The study conducted at a tertiary referral ophthalmic center in India has reported that the incidence of the disease was one in 135–200 ophthalmic patients in India. However, recent years have witnessed a decrease in the incidence of the disease. The disease has a characteristic clinical picture, fluorescein angiographic finding and natural course. The disease, which occurs in young healthy adult males, initially presents as retinal periphlebitis and later as retinal ischemia, leading to vascular alterations and neovascularization.
Recurrent vitreous hemorrhage with or without retinal detachment is the common sequelae. Role of human leukocyte antigen, retinal autoimmunity, mycobacterial tuberculosis genome has recently been found. Recent molecular biological studies by the author and group have found mycobacterial tuberculosis genome in the vitreous and epiretinal membrane specimens of affected patients. The management options include oral steroid in active inflammatory stages, laser photocoagulation in retinal neovascularization and pars plana vitrectomy in vitreous hemorrhage. Retinal vasculitis can also occur in several collagen vascular diseases like systemic lupus erythematosus, Wegener’s granulomatosis, polyanterior nodosis, Churg-strauss syndrome (allergic granulomatous angiitis), relapsing polychondritis and rheumatoid arthritis.

**Tubercular uveitis**

Tubercular uveitis is relatively common in tuberculosis endemic countries like India. It has protean manifestations and can present as granulomatous uveitis with mutton-fat keratic precipitates, iris nodules, broad posterior synechia, intermediate uveitis, subretinal abscess, multifocal serpiginoid choroiditis and retinal vasculitis. The disease is extremely paucibacillary. Intraocular fluids, like aqueous and vitreous, rarely show acid fast bacilli. Culture for mycobacterial tuberculosis is often negative. However, nested and real time PCR show mycobacterial tuberculosis DNA in such uveitis.

The disease occurs by dissemination of mycobacterium tuberculosis from the lungs. However, it is still not clear whether the disease occurs due to direct infection of mycobacterium tuberculosis or immune-mediated reaction of tubercular antigen. Rao et al. have found that retinal pigment epithelium harbors acid fast bacilli in tubercular uveitis. Mycobacterium tuberculosis H37Ra was shown to be phagocytosed in human RPE cell cultures. Authors have reported five cases of intraocular tuberculosis where acid fast bacilli were seen in intraocular fluid or eviscerated tissue of the patients. However, such cases are rare.

Tagirasa et al. have demonstrated autoreactive T cells in tuberculosis-associated uveitic eye. These cells are relatively resistant to activation-induced cell death. The diagnosis of tubercular uveitis is made by the clinical suspicion supported by laboratory test like tuberculin sensitivity test, interferon gamma release assay, chest radiography, and high resolution computerized tomography of the chest. Four drugs anti-tubercular therapy are recommended for tubercular uveitis. Duration of such treatment should be nine months instead of six months, which is usually followed for pulmonary tuberculosis.

**Toxoplasmic retinochoroiditis**

Toxoplasmic retinochoroiditis is one of the common causes of posterior uveitis. It is caused by the parasite *Toxoplasma gondii* (*T.gondii*). Most of the patients with ocular toxoplasmosis present with posterior uveitis in their second to fourth decade of life. Humans and other mammals are intermediate hosts, and cats are the definitive host for *Toxoplasma gondii*.

Ocular toxoplasmosis is transmitted orally by consumption of food or beverages contaminated with tissue cyst or oocyst. Contamination of water with feline feces can lead to outbreak of toxoplasmosis in communities, as seen few years back in Coimbatore, India. Congenital transmission of *T.gondii* occurs by trans placental spread of *T.gondii* tachyzoite. *T.gondii* can also spread via blood transfusion and organ transplantation.

A recent study from India has found a seroprevalence of 45% for toxoplasma-specific IgG antibodies. A study of the seroprevalence of *T. gondii*-specific IgG antibodies from northern India has found an overall prevalence of 51.6% in males and 89.2% in females. The author and co-workers have identified that posterior uveitis toxoplasma was the most common infectious etiology and the prevalence was 27%. Meenken et al. have found an increased frequency of HLA-Bw62 antigen in patients with ocular toxoplasmosis.

**Viral retinitis**

Several viruses can affect the retina. These include human herpes viruses, measles, rubella, dengue, West Nile, chikungunya, influenza and Zika virus. It can affect patients with immunocompromised conditions like AIDS, organ transplantation, and malignancy as well as immune competent subjects. Some of the viral infections progress very rapidly and cause several visual morbidities. The study conducted by the author and co-workers have found that only 45% has favorable visual outcome in acute retinal necrosis.

Viral retinitis can occur with or without systemic involvement. Some viral retinitis like acute retinal necrosis and progressive outer retinal necrosis extend very rapidly and cause severe visual morbidity. Many viruses remain latent in host and manifest later. Many factors like virulence of the virus, host immunity, age and comorbidities influence...
reactivation of viral infection in the posterior segment.

**Conclusion**

Uveitis is an enigmatic disease with protean manifestation and varied etiology. The knowledge regarding exact pathogenesis of this disease is still evolving. Precise treatment is still not available in many of the uveitic diseases. Future research will unravel many of the mysteries of this disease.

**Competing interests**

The author declares that he has no competing interests.

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*Correspondence: Dr. Jyotirmay Biswas drjb@snmail.org

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