UVEITIS: DIAGNOSIS AND MANAGEMENT

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Uveitis is a generic term which describes inflammation of the uvea, and of the retina and retinal vessels, and as such gives no clue as to the pathogenesis or prognosis for vision. The uvea consists of the iris, ciliary body and choroid, and is so named for its dark grape-like appearance, which is caused by its heavy pigmentation and high vascularity. Uveitis has an incidence of only 17/100,000 of the population,[1] but is responsible for 10% of those registered legally blind or partially sighted under the age of 65. [2] This is likely to be an underestimate as more frequently the complications of uveitis are often recorded on the blind registration form rather than the original diagnosis.

The clinical spectrum is wide. The characteristics of a particular uveitic entity allow it to be put into categories that can provide information on natural history and prognosis for vision. A number of classifications exist, and these are usually used together to characterise a particular uveitic condition.

UVEITIS: CLUES TO DIAGNOSIS

1. Where is the inflammation located in the eye?
2. Is the disease acute or chronic?
3. Is the disease unilateral or bilateral?
4. What are the demographic features (e.g. age, sex, ethnicity) of the patient?
5. What associated symptoms and signs does the patient have?
6. How did the disease respond to previous therapy?[3]

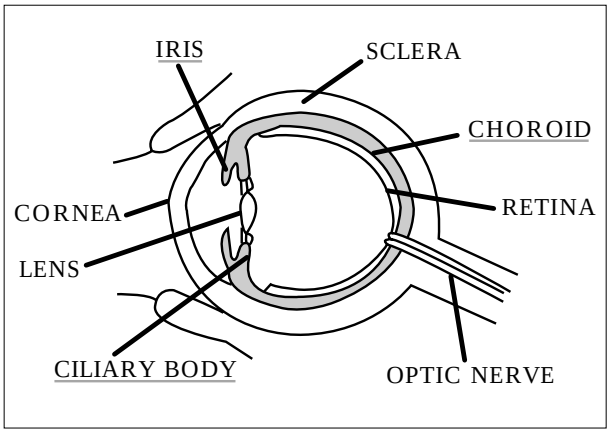

FIGURE 1[4]
Diagram of the eye to show the Uvea

CLINICAL FEATURES

Anterior Uveitis

The International Uveitis Study Group[5] recommends that patients be classified according to the location of pathology within the eye. Anterior uveitis describes inflammation that is mainly limited to the anterior segment, i.e. iritis, anterior cyclitis and iridocyclitis. It is the most common type of uveitis and was shown to be responsible for 90% of uveitis seen by community-based ophthalmologists in the US.[6] Patients with anterior uveitis usually present with a history of redness, pain and watering in the eye, with some accompanying blurring of vision. In some cases, notably chronic uveitis entities such as those associated with pauciarticular Juvenile Chronic Arthritis and Fuchs' heterochromic cyclitis, the uveitis may be asymptomatic.

On examination visual acuity is typically reduced, and there are ciliary injection, keratic precipitates, anterior chamber cells and flare. The anterior chamber cells and flare are as a result of the breakdown in the blood/aqueous barrier; severe anterior chamber inflammation may result in fibrin deposition, posterior synechia (iris-lens adhesions causing an irregular, often petalloid pupil) and a hypopyon. Keratic precipitates are aggregates of inflammatory cells that coat the corneal endothelium. They vary in appearance from small 'stellate' precipitates distributed over the whole cornea to large 'mutton-fat' precipitates.

Acute anterior uveitis

Acute anterior uveitis is of sudden onset and usually resolves within three months. It may occur once and resolve completely, or there may be recurrent episodes. It may be unilateral or bilateral; patients with recurrent episodes may have inflammation in either eye. An infective agent may be the underlying cause, or the uveitis may be non-infectious in origin (often presumed to be autoimmune). The most common infectious causes are *Herpes simplex* and *Herpes zoster*. Following surgery or trauma (such as a corneal ulcer), bacterial or fungal infection may also present as an anterior uveitis. It is important to identify this complication early and to treat it aggressively with anti-microbials to avoid endophthalmitis and blindness. Non-infectious uveitis may be induced by the crystalline lens or by blunt trauma; it may occur as part of a recognised ocular syndrome or as part of a systemic disease, and may also be idiopathic.

Acute anterior uveitis associated with HLA-B27

In a Caucasian population acute anterior uveitis is associated with HLA-B27 in 50% of patients.[7] Features said to be typical of HLA-B27-associated uveitis are: a tendancy to recurrence, severe anterior chamber activity during an attack, absence of mutton fat keratic precipitates, an age at onset less than 40 years, and associated sero-negative arthropathy. In 73 patients with HLA-B27-positive acute anterior uveitis 51% had an associated sero-negative spondyloarthropathy (ankylosing spondylitis 39%, Reiter's syndrome 8% or psoriatic arthropathy 4%) as compared to only 1% of a group of HLA-B27-negative patients with acute anterior uveitis. The systemic disease is often undiagnosed before the onset of uveitis.[8]

Chronic anterior uveitis

Chronic anterior uveitis lasts longer than three months although it may be initally acute in onset. Such patients are more likely to have asymptomatic episodes and to suffer sight-threatening complications. A review of 400 patients demonstrated that 51% had idiopathic disease even after extensive investigation.[9] The most common associations are *Herpes simplex* infection, HLA-B27, sarcoidosis, Juvenile Chronic Arthritis, Fuchs' heterochromic iridocyclitis, trauma and surgery.

Chronic uveitis of any variety may be associated with corneal calcium deposition resulting in band keratopathy; and this complication is common with the chronic uveitis associated with Juvenile Chronic Arthritis, in which condition the risk was shown to be greatest in sero-negative, antinuclear antibody-positive girls with a pauciarticular onset of disease. Screening is important to reduce the sight-threatening complications.[10]

Acute Anterior Uveitis: Typical Symptoms

- Blurred vision
- Red eye
- Watering
- Photophobia

Acute Anterior Uveitis: Typical Signs

- Reduced Visual Acuity
- Injection
- Anterior Chamber Cells & Flare

Intermediate uveitis

Intermediate uveitis describes inflammation of the vitreous, pars plana and peripheral retina, and is most common in young adults; it may occur in children and the elderly. Involvement is usually bilateral but may be markedly asymmetrical. The characteristic symptom is an increase in floaters (mobile opacities in the visual field). Examination may reveal vitreous cells, opacities, 'snowballs' (collections of inflammatory cells) and 'snowbanks' (fibroglial proliferation at the pars plana, secondary to inflammation). Macular oedema is a common complication and results in blurring of vision. Vitreous haemorrhage from peripheral neovascularization occurs rarely. Chronic, idiopathic, intermediate uveitis with snowbanks is known as 'pars planitis'.

Thirty per cent of patients with intermediate uveitis had an associated condition[9] and none of these had unilateral disease. Systemic associations include sarcoidosis, multiple sclerosis and Lyme disease.

Intermediate Uveitis: Typical Symptoms

- Floaters
- Blurred Vision

Intermediate Uveitis: Typical Signs

- Vitreous Cells
- Vitreous Opacities
- Snowballs
- Macular oedema

Posterior uveitis

Posterior uveitis may be focal, multifocal or diffuse. It referred to a named choroiditis, chorioretinitis, retinochoroiditis or neuroretinitis depending on the predominant ocular site of inflammation. Spill-over of the inflammation into the vitreous is common, and in such instances, patients may complain of floaters and visual disturbance. The aetiology may be infectious or non-infectious; an infectious aetiology (bacterial, fungal, parasitic or viral) is more likely in the posterior segment. Debilitated patients who have a systemic infection such as septicaemia or disseminated fungal infection are at risk of a metastatic endophthalmitis. The non-infectious posterior uveitides may either be of an immune origin or of unknown aetiology. A number of local and systematic conditions may masquerade as posterior uveitis.

Toxoplasmosis

This focal necrotizing retinitis is caused by the intracellular parasite *Toxoplasma gondii*. Worldwide, it is an important cause of posterior uveitis and a significant cause of visual handicap. Cats who are the primary hosts excrete infectious oocytes in their faeces for 14 days after becoming infected and these may remain infective in soil for up to 18 months. Cows, sheep and pigs act as intermediate hosts. Human infection can result secondary to the ingestion of encysted forms in rare or partially cooked meat.

Ocular toxoplasmosis may occur both as a reactivation of congenital infection or secondary to acquired infection, the latter being more common than previously thought. The ratio of congenital to acquired infection probably varies from country to country.[11] Patients present with blurred vision or floaters. Examination reveals a dense vitritis with a focal necrotizing retinitis with involvement of the surrounding retinal vessels. The condition is self-limiting in immunocompetent hosts and healing leads to a pigmented chorioretinal scar. Reactivation may occur at the edge of old scars.

'Birdshot' chorioretinopathy

This is an uncommon condition that most typically occurs in Caucasian females in the fifth decade. Patients gradually develop blurred vision, night blindness and defects in colour vision. The clinical features are characteristic with multiple depigmented spots which are scattered over the fundus in the chronic stage. A useful ancillary test is HLA typing as over 90% of patients with this condition are HLA-A29 positive, whereas the frequency of this haplotype in the general Caucasian population is 7%. The strength of this association is exceeded only by narcolepsy, which has a 100% association with HLA-DR2 compared with the incidence 21.5% in the normal population.[12] The course of the disease is chronic with exacerbations and remissions.

Panuveitis

Panuveitis describes inflammation involving all segments of the eye. It tends to run a chronic course, and may be part of a systemic disease or be only localised to the eye; it may be idiopathic or of infectious aetiology. The most common associations are sarcoidosis, Behçets disease, sympathetic ophthalmia and Vogt-Koyanagi-Harada syndrome.

Sarcoidosis

This idiopathic, multisystem, granulomatous, inflammatory disorder affects all segments of the eye and 25-50% of patients with systemic sarcoidosis will have ocular signs. Ocular sarcoidosis may also occur in isolation.

Granulomatous uveitis is the most common presentation; involvement of the anterior segment is more likely than involvement of the posterior segment, and chronic uveitis is common. Typical anterior segment signs are bilateral mutton fat precipitates and iris nodules on the iris surface (Busacca nodules), at the pupil margin (Koeppe nodules) or in the anterior chamber angle. The posterior manifestations are a marked periphlebitis with an appearance described as 'candle-wax drippings', vitritis with snowballs and choroidal lesions.

Behçet's syndrome

This multisystem disorder is characterised by genital and aphthous ulcers, and can be manifested by arthritis and recurrent, explosive, intraocular inflammation secondary to an occlusive vasculitis. The diagnosis is a clinical one and internationally accepted diagnostic criteria exist.[13] Ocular involvement occurs in 78.6%[14] of patients, and vasculitis may lead to irreversible retinal damage, neovascularization and secondary glaucoma. Despite aggressive therapy useful vision may be lost within 10 years of diagnosis in up to three-quarters of involved eyes.[15]

Sympathetic ophthalmia

This is a rare, bilateral, granulomatous panuveitis that occurs after injury or surgery to one eye. It is hypothesised that release of previously sequestered antigens from within the injured eye leads to an autoimmune response in the fellow 'sympathising' eye. In 56% of patients inflammation in the sympathising eye occurs within one year but it may occur from days to decades after the insult.[16] There is anterior chamber inflammation with vitritis and the mid-periphery has multiple pigmented chorioretinal scars known as Dalen-Fuchs nodules. Sympathetic ophthalmia may lead to bilateral blindness but early-onset, long-term aggressive immunosuppression is usually effective in maintaining vision.

Vogt-Koyanagi-Harada syndrome

This bilateral panuveitis is often similar in ocular appearance to sympathetic ophthalmia but is associated with neurological and cutaneous signs. There may be prodromal headache, stiff neck and vertigo; CSF examination at this time reveals pleocytosis. Deafness may also occur. Vitiligo, poliosis and alopecia are late signs. Exudative retinal detachment, and swollen, hyperaemic optic discs are typical in the acute phase. Peripheral Dalen-Fuchs-like nodules are also seen. Inflammation may be acute and resolve rapidly after treatment, or there may be a chronic course, particularly when there is optic nerve involvement. Pigment mottling and depigmentation are typical in the chronic phase.

'Masquerade' syndromes

Syndromes masquerading as uveitis will not respond well to treatment for uveitis, and non-response should trigger a search for an alternative diagnosis. This is particularly true of the elderly as immune-mediated uveitis is less common in this age group. Examples of conditions that may masquerade as intraocular inflammatory disease include malignant conditions such as intraocular neoplasms, lymphoma and leukaemia, and non-malignant conditions such as retinal detachment.

DIAGNOSIS

Often, the clinical opthalmological appearance of a particular uveitic entity is characteristic and investigations may not be required to make the diagnosis. When investigations are carried out they must be tailored to the type of uveitis and to the patient. The proportion of patients that can be classified into distinct clinical entities following investigation will vary depending on the referral base; the remainder are termed idiopathic. When a systemic condition is suspected collaboration with physicians is advisable to help to establish (or eliminate) the diagnosis and to determine the management strategy. Colour photographs can be used to follow the course of the disease process as can fluorescein angiography. Intravenous injection of fluorescein dye is particularly useful to demonstrate macular oedema which appears as late leakage of the dye in the macular region.

Ocular sampling is reserved for use in patients with severe intra-ocular inflammation that is thought to be either infective or malignant in origin, as it does not assist with the diagnosis of the different immune-mediated inflammations. Samples are obtained from aqueous and / or vitreous fluids. Microscopy, culture and sensitivity testing for bacteria and fungi and / or polymerase chain reaction techniques for herpes viruses and toxoplasma can be performed. Cytology can also confirm a diagnosis of malignancy. Because of the small volume of sample that can be reasonably collected, the tests requested must be carefully tailored to the patient.

Skin and / or conjunctival biopsy may be useful in the diagnosis of leprosy, onchocerciasis and sarcoidosis. Although only 12% of patients with suspected sarcoidosis would have a positive result on blind biopsy, the test has the advantage of being relatively non-invasive; a biopsy of suspicious lesions will improve the yield. Lacrimal gland biopsy, once commonly suggested, frequently results in permanent damage to the lacrimal ductules and is therefore not recommended.

MANAGEMENT

Management depends on the type of uveitis and on the characteristics of the particular patient. When an infectious aetiology has been identified, treatment can be directed against this agent, although concurrent immunosuppression to minimise ocular damage is usually required. In most uveitides the aetiology is thought to be non-infectious or immune-mediated, and therefore immunosuppression is the mainstay of treatment. Sight-threatening and systemic complications of the uveitis and its treatment must also be actively identified and managed. Treatment may be topical, periocular, intraocular, systemic or surgical depending on the condition.

Anterior uveitis

Topical corticosteroids and mydriasis are the mainstay of treatment for anterior segment inflammation. Treatment is initially intensive with the frequent instillation of potent formulations, but can then be tapered slowly according to ocular response. Poor compliance will lead to relapse or a poor response.

Complications of topical steroids include posterior subcapsular cataract, raised intraocular pressure and *Herpes simplex* keratitis. Steroid treatment should therefore be managed by ophthalmologists.

Intermediate and posterior uveitis

Steroid therapy is the main and first line treatment, and can be administered topically or systemically. Topical therapy does not penetrate into the posterior segment of the eye and periocular delivery of steroids are the treatment of choice for the treatment of unilateral intermediate and posterior segment inflammation.[17] The most common routes of injection are below Tenon's capsule and onto the orbital floor. The posterior subtenon's approach is particularly useful for the treatment of macular oedema as the drug is delivered directly over the macular region. Depot steroids such as depomedrone and triamcinolone are used as these are absorbed gradually into the eye over a period of time. The systemic side-effects of steroids are therefore minimised. It may take up to four weeks for a clinical response to be evident. A local steroid effect with minimal systemic side-effects is particularly useful in the treatment of pregnant women and children, and the procedure, if necessary, can be carried out under general anaesthetic. Risks of periocular injection include perforation of the globe, which is rare with a careful technique, and raised intraocular pressure. Intraocular pressure must be carefully monitored following injection, as there may be a dramatic rise that is difficult to manage.[18] Patients in whom topical or systemic steroids produce a rise in intraocular pressure (steroid responders) should NOT receive depot injections.

Systemic steroids are used in the treatment of bilateral and sight-threatening disease.[19] The starting dose must be sufficiently high to suppress inflammation, and doses of 1mg/kg/day of prednisolone are often used. After the initial high dosage, the steroid can be tailed off slowly titrating clinical response against dose. Reactivation requires a return to high dose. The risk / benefit balance of therapy must be discussed with patients before starting treatment, and in view of the possible side-effects systemic steroids should not be considered for inflammation that is not sight-threatening. If an infectious agent such as toxoplasma or a mycobacterium has been identified, the relevant anti-microbial cover is required to avoid fulminating infection. Patients should be made aware that treatment might be long-term and recurrent. High dose intravenous methylprednisolone is effective for severe sight-threatening uveitis[20] but although the response is rapid, it is short-lived and associated with an increased risk of anaphylaxis, circulatory collapse and death.

If doses of steroids greater than approximately 15mg/day of oral prednisolone or equivalent are required to control disease relapse or if toxicity is limiting adequate dosage for long term management, then second line steroid-sparing agents are needed. Combination therapy allows more effective control of a severe uveitic process as well as allowing the gradual reduction of steroids whilst maintaining a therapeutic remission.[21] The drugs used include cyclosporin, azathioprine, methotrexate, mycophenolate mofetil, tacrolimus, and more rarely, cyclophosphamide and chlorambucil. Unlike steroids these drugs do not have an immediate onset of action, and high dose steroid therapy must be maintained until they become effective. Cyclosporin and tacrolimus have the advantage that they specifically target T-cell activation and in most non-infectious posterior uveitides, T-cell activation is central to the initiation of inflammation. Immunosuppressants vary in their mechanisms of action and side-effect profiles so treatment must always be tailored to an individual patient and situation.

Complications of uveitis occur in spite of medical treatment and reversible causes for loss of vision must be identified and treated aggressively. A retrospective study of 582 patients attending university ophthalmology clinics with uveitis found that complications occurred in 55% and 23% who underwent one or more surgical procedures.[2]

Cataract, glaucoma, and cystoid macular oedema are the most frequent sight-threatening complications.

Cataract surgery with intraocular lens implantation was a high-risk procedure but current peri-operative management regimens have greatly improved the outcome.[22] Intraocular inflammation must be minimised before surgery, and immunosuppression is increased perioperatively.

Regular screening for glaucoma is important as this may result as a complication of steroid use or of the uveitic process itself and may be difficult to treat. For most patients, secondary glaucoma can be satisfactorily managed with topical medication alone. Surgical options include trabeculectomy with adjunctive anti-metabolites to reduce scarring and improve outcome, filtering tubes and, in the end stage, cyclodestructive procedures for pain.

Vitreous inflammation may lead to posterior vitreous detachment and vitreous opacification. These may cause traction leading to tractional or rhegmatogenous retinal detachment that requires vitreoretinal surgery. Exudative retinal detachments such as those occurring in Vogt-Koyanagi-Harada syndrome flatten spontaneously when the inflammation resolves.

PROGNOSIS

Improvements in the visual morbidity following uveitis have been seen following better management. In Juvenile Chronic Arthritis, for example, screening of patients and earlier, more aggressive treatment have led to a significant reduction in morbidity with only 12% of affected eyes now becoming blind.[23] Increasing understanding of the pathophysiology of the various types of uveitis should lead to more specific treatment options and further improvement in the prognosis.

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