Regular review

Management of chronic uveitis

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To many, uveitis is an acute problem that resolves after treatment with topical corticosteroids. While this may be true of acute anterior uveitis, many forms of uveitis are chronic in nature and often require continuous treatment. The uveitis may be anterior, posterior, or both, and there can be considerable ocular morbidity. Of people aged under 65 who are registered legally blind, 10% are visually compromised because of uveitis and its complications—very nearly the same number affected by diabetic retinopathy.[1 2] Given that uveitis is a much rarer disorder than diabetes (about 250 times less common), this gives some indication of the severity of the problems that can occur. This article describes the management of chronic uveitis, including its diagnosis and differential diagnosis, indications for and types of treatment, and the management of complications.

Summary points

- Intraocular inflammation has various causes and can be acute or chronic
- In either case the inflammatory process can be apparently localised to the eye or be part of a systemic disease such as sarcoidosis or Behçet's disease
- The inflammation can occur in any part of the eye—anterior, posterior, or both—and visual loss can occur with any type
- Treatment depends on the location and severity of the inflammation, with systemic drugs being reserved for sight threatening posterior disease
- Complications are common and include cataract, glaucoma, macular oedema—all of which can reduce vision

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Types of disease

Chronic uveitis encompasses a heterogeneous group of diseases, many of which are idiopathic in origin.[3] Systemic diseases, including sarcoidosis and Behçet's syndrome, can be associated with either acute or chronic uveitis. Chronic uveitis can be differentiated from acute recurrent anterior uveitis by its rate of progression[4] and can usefully be defined as active uveitis that persists longer than three months. Chronic uveitis is associated with a high incidence of vision threatening complications such as cataract, macular oedema, and, most importantly, glaucoma, which may cause irreversible visual loss.

Differential diagnosis

Chronic uveitis can be classified anatomically as anterior, intermediate, or posterior, or panuveitis. Box 1 lists the common causes of chronic uveitis and details key clinical features which help to differentiate each type. The aetiological diagnosis of chronic uveitis rests on the patient's history, clinical signs, and a careful systems review, combined with the results of a few selected investigations.

Chronic anterior uveitis is insidious in onset, persistent, associated with a high incidence of visually threatening complications, and has a variable long term visual prognosis. It is most often idiopathic but can be associated with systemic diseases such as juvenile chronic arthritis, Behçet's disease, and sarcoidosis.

Intermediate uveitis is characterised by floaters and blurred vision and varies in severity. The inflammation consists of vitreous cells associated with a variable degree of macular oedema and swelling of the optic disc without focal choroidal or retinal pathology.[5] It is often idiopathic in origin, but may be associated with multiple sclerosis, sarcoidosis, syphilis, Lyme disease, and ocular lymphoma.

Posterior uveitis, which has a range of clinical appearances, is often chronic and may be associated with many systemic diseases—including sarcoidosis, syphilis, Behçet's syndrome, Vogt Koyanagi Harada syndrome—and purely ocular syndromes such as sympathetic ophthalmia and birdshot chorioretinopathy.[6–9] It is essential to carefully consider the possibility of an infectious cause for chronic posterior uveitis.

Association with systemic diseases

In Britain sarcoidosis is the commonest systemic disease that presents as chronic uveitis. It has protean ocular manifestations and may present with a spectrum of ocular signs, including anterior and posterior uveitis, retinal vascular sheathing, and optic disc abnormalities.[7] In Japan Behçet's disease is the commonest systemic

Box 1: Common causes of chronic uveitis and their distinguishing clinical features

Anterior uveitis

- Fuchs' heterochromic cyclitis
  Uniocular; variable low grade uveitis; characteristic keratitis precipitates extending above horizontal meridian of cornea; not responsive to topical steroids; iris abnormalities; no synechiae; vitreous abnormalities
- Juvenile chronic arthritis
  Onset in childhood; bilateral; typically severe; resistant to treatment; antinuclear antibodies present, rheumatoid factor absent
- Sarcoidosis
  Unilateral or bilateral; persistent low grade inflammation; iris nodules
- Herpetic keratouveitis
  Unilateral; sector iris atrophy; corneal abnormalities; raised intraocular pressure
- Chronic idiopathic anterior uveitis
  Unilateral or bilateral; severe; resistant to treatment; idiopathic; high rate of complications
- Masquerade syndromes
  Iris infiltration; hypopyon; poor response to treatment; elevated intraocular pressure

Intermediate uveitis

- Intermediate uveitis and pars planitis
  Variable anterior chamber reaction; occasional acute onset; vitreous cells, snowballs and snowbanks; no focal retinal or choroidal pathology; macular oedema, optic disc swelling, retinal oedema; peripheral neovascularisation

Posterior uveitis

Infective

- Syphilis
  Positive syphilis serology; optic disc involvement; abnormal cerebrospinal fluid; systemic signs and symptoms
- Tuberculosis
  High risk factors—HIV infection, malnutrition, immunosuppression; multifocal choroiditis; systemic illness
- Lyme disease
  History of exposure; arthropathy and cranial neuropathy; optic disc involvement; positive serology; abnormal cerebrospinal fluid
- Fungal
  High risk factors—intravenous drug misuse, central venous catheters, major illness; often delayed onset after serious systemic illness or sepsis
- Viral
  High risk factors—HIV infection, immunosuppression; cytomegalovirus retinitis, commonest in patients with AIDS; herpetic retinitis (varicella zoster virus or herpes simplex virus) commonest in other groups
- Parasitic
  Ocular toxocariasis produces unilateral chronic panuveitis associated with granulomatous mass lesion in fundus (ocular toxoplasmosis usually causes acute retinochoroiditis)

Systemic

- Vogt Koyanagi Harada syndrome
  Neurological prodrome; profound visual loss; unusual pink swollen optic discs; multiple choroidal lesions; exudative retinal detachments; late onset poliosis and vitiligo
- Behçet's disease
  Racial predisposition; florid progressive occlusive retinitis, vasculitis, and severe panuveitis; hypopyon; mouth ulcers and genital ulcers; systemic vasculitis
- Sarcoidosis
  Unilateral or bilateral; retinal vasculitis; optic disc involvement; choroiditis

Endogenous

- Birdshot choroidopathy
  Older age group; panuveitis; subtle punched out white non-pigmented choroidal lesions, typically nasal and posterior pole; macular oedema and disc swelling; positive HLA-A29
- Serpiginous choroidopathy
  Relentless course; media apparently not affected; slowly enlarging pigmented chorioretinal lesions; peripapillary location; acute exacerbation
- Multifocal choroiditis with panuveitis
  Multiple punched out chorioretinal scars in fundus; variable panuveitis
- Sympathetic ophthalmia
  History of trauma or surgery; bilateral panuveitis; chorioretinal lesions; serous retinal detachments

Masquerade

- Lymphoma
  Vitreous or retinal infiltration; poor response to treatment

disease associated with chronic uveitis, and in other parts of the world it may be tuberculosis.[10]

Several purely ocular syndromes cause posterior uveitis. Sympathetic ophthalmia is a bilateral panuveitis occurring after penetrating trauma or intraocular surgery.[8] Multiple chorioretinal scars with panuveitis suggest multifocal choroiditis, and both birdshot chorioretinopathy and serpiginous choroidopathy are important to recognise as they are not associated with systemic disease.[9]

Intraocular lymphoma may present as a chronic uveitis in older patients, especially when there is vitritis and vitreous veils and a poor response to treatment. Intraocular tumours, particularly retinoblastoma in children, may also occasionally present in this manner.

Investigations

The only investigations that should be performed in all patients with chronic uveitis are a chest *x* ray, angiotensin converting enzyme, and syphilis serology, as the results of these investigations may substantially affect long term management. Screening with a broad battery of investigations has a low diagnostic yield, whereas careful history taking with relevant examination is much more important. Box 2 lists important investigations and their indications. In patients with apparent idiopathic disease, an open mind needs to be

kept about aetiology. New symptoms or signs such as arthralgia or erythema nodosum should prompt further directed investigations.

Managing chronic uveitis

Patients are followed up regularly to determine disease activity, ocular complications, and side effects of treatment. There are many causes of reduced vision in such patients and not all need increased anti-inflammatory treatment. The follow up schedule is individualised according to the aetiology of the uveitis and its activity, the threat to vision, and type of treatment required.

Indications for treatment

Specific infectious causes of chronic uveitis such as syphilis, Lyme disease, and viral retinitis are treated with appropriate antimicrobial therapy and the judicious use of corticosteroids. The long term treatment of patients with non-infectious chronic uveitis is similar in most patients despite the wide spectrum of possible aetiologies as it is determined by the type of complications.

The aims of treatment are to control inflammation, prevent visual loss, and minimise long term complications of the disease and its treatment. Macular oedema is the commonest indication for treatment. Treatment is usually indicated if the visual acuity has fallen to less than 6/12, or if the patient is experiencing visual difficulties. In patients with longstanding macular oedema and poor vision or where it is not possible to determine easily the cause of visual loss, a trial of immunosuppressive treatment is usually indicated to determine whether the visual loss is reversible. Many patients with unilateral chronic uveitis can be managed with topical corticosteroids to control anterior uveitis and periocular corticosteroids for macular oedema and visual loss. Patients with useful vision in only one eye must be managed aggressively to control inflammation and preserve vision.

Topical treatment

Long term topical corticosteroids are the mainstay of treatment for chronic anterior uveitis. Regular use of mydriatics ensures that the pupil is kept relatively dilated and limits formation of synechiae, which may lead to earlier cataract formation and elevated intraocular pressure.

Periocular corticosteroids

Periocular corticosteroids may be administered via a posterior subtenons or orbital floor approach.[11] They are contraindicated in patients with a history of glaucoma or corticosteroid induced elevation of intraocular pressure. If a beneficial response is achieved, further injections can be given when necessary. Periocular corticosteroids can be used safely in all age groups, but young children may require sedation or general anaesthesia before injection. Bilateral periocular treatment may be indicated instead of systemic corticosteroids in some patients including children, during pregnancy, and in patients with diabetes or with psychiatric illness.

Treatment failures in patients with unilateral chronic uveitis should be assessed carefully as further treatment necessitates the use of systemic drugs. The risks and benefits of long term systemic treatment with corticosteroids and other drugs for uniocular disease must be carefully evaluated and discussed with the patient.

Box 2: Useful investigations for chronic uveitis

Chest x ray—Diagnosis of tuberculosis, sarcoidosis, lymphoma, lung carcinoma

Syphilis serology—Diagnosis of syphilis

HLA-A29—Diagnosis of birdshot chorioretinopathy

Mantoux test—Anergic response despite prior BCG vaccination is consistent with sarcoidosis. Strong positive response without prior vaccination suggests exposure to tuberculosis

HIV serology—If patient of high risk status or clinical picture suggests HIV related uveitis such as cytomegalovirus retinitis

Lyme disease serology—If patient from endemic area or with history of exposure and suggestive symptoms

Antinuclear antibodies—If clinical picture suggests juvenile chronic arthritis

Aqueous and vitreous biopsies—Diagnosis of infective endophthalmitis and intraocular lymphoma

Systemic corticosteroids

Corticosteroids are the mainstay of systemic treatment for patients with chronic uveitis, and the usual indication for treatment is the presence of macular oedema and visual acuity of less than 6/12.[12 13] Patients should be treated with appropriate doses to determine whether the macular oedema is reversible. Thus maximum treatment (1.0-1.5 mg/kg body weight/day of prednisone or prednisolone) should be used for two to three weeks. If there is no response at this dose, addition of a second line agent such as cyclosporin (or azathioprine or mycophenolate in older patients) for a further four to six weeks may be considered. In children the doses should be adjusted appropriately.

If there is a response to corticosteroids the dose is tapered by 5 mg a week until the lowest dose that maintains the vision is determined. If this dose is ≤ 15 mg/day it is not usually necessary to add a second agent, but if frequent relapses occur at the maintenance dose a second drug may be indicated. Such patients usually require maintenance corticosteroid treatment, and periodic attempts should be made to try to lower the dose. All patients receiving systemic corticosteroids should be regularly reviewed and assessed for side effects, particularly diabetes, hypertension, and osteoporosis.

Other systemic immunosuppressive therapy

If macular oedema recurs and visual acuity decreases at an unacceptably high dose of corticosteroid (>15 mg/day of prednisolone) an additional drug is necessary to help control the inflammation. Cyclosporin is the drug of choice for most patients aged under 50 years.[12 13] The commonest dose limiting side effects of cyclosporin are hypertension and renal dysfunction, which are usually reversible if the drug is stopped.

Several other drugs can be considered in patients who require additional immunosuppressive therapy when cyclosporin is not appropriate or not tolerated. Azathioprine, methotrexate, and, much less commonly, cyclophosphamide are the most used, but each is associated with important side effects and complications.[14] Other agents such as mycophenolate, tacrolimus, and

Box 3: Complications of chronic uveitis and their management

Macular oedema
- Periocular steroids
- Systemic steroids
- Immunosuppressive drugs

Cataract
- Surgery once uveitis controlled for 3 months preoperatively
- Perioperative cover with corticosteroid
- Intraocular lens in most patients

Glaucoma
- Management depends on type
  Topical drugs
  Short term treatment with systemic carbonic anhydrase inhibitors
  Surgery

Synechiae
- Minimise with regular mydriatics

Band keratopathy
- Chelation with EDTA
- Excimer laser

Vitreous opacities
- Observation
- Occasionally short course of corticosteroids
- Vitrectomy rarely required

Vitreous haemorrhage
- Observation
- Exclude new vessels and retinal tear as cause

Retinal neovascularisation
- Control uveitis
- Laser photocoagulation if ischaemia present

Subretinal neovascularisation
- Observation
- Laser photocoagulation
- Interferon a
- Surgical membranectomy

Retinal detachment
- Determine whether exudative, rhegmatogenous, or traction
- Surgery usually involves vitrectomy
- Perioperative cover with corticosteroid

humanised Tac monoclonal antibodies have been used.[15 16 17] The decision to start treatment with immunosuppressive drugs is a long term commitment by both the clinician and patient, as treatment is likely to last for a minimum of six months and is often much longer.

Complications of chronic uveitis

Complications from chronic uveitis are common and may result in severe visual loss. Box 3 lists the common complications and summarises the principles of management.

Macular oedema can complicate any type of uveitis and can cause substantial visual loss.

Cataract is common in chronic uveitis and its treatment with corticosteroids. Techniques for cataract surgery and perioperative management have improved greatly, and most patients with uveitis are now suitable for intraocular lens implantation and do well.[18]

Glaucoma is the most overlooked complication of chronic uveitis and has several causes.[19] Medical management with topical agents such as β blockers control the elevation of intraocular pressure in most patients. Some patients also require oral carbonic anhydrase inhibitors, while surgical intervention is reserved for those who have progressive visual loss or uncontrollable intraocular pressures.

Surgery

Surgery may be required for complications such as cataract, glaucoma, and vitreoretinal problems, but, except in emergency situations, it should be contemplated only once the uveitis is controlled, ideally for at least three months. Intraocular surgery (cataract removal, vitrectomy, and retinal detachment surgery) is performed under the cover of systemic corticosteroids to prevent a relapse of uveitis. Removal of the vitreous body (vitrectomy) may be helpful when there is substantial opacity but also may improve disease control, particularly in younger patients.

Visual aids

When patients lose vision permanently from the complications of uveitis, many can be helped by the use of aids for low vision.[20] Various aids are available and can be used both for distance and near vision. With them, many patients are able to continue to work and remain independent. Such patients may also benefit from counselling and attending retraining centres for the visually handicapped.

Future developments

Application of molecular biological techniques such as the polymerase chain reaction to ocular fluids and tissues from patients with chronic uveitis are likely to improve our understanding of the pathogenesis of uveitis, with the prospect of more selective treatments. Systems for local delivery of drugs are being developed—similar to those used to release ganciclovir into the eye for cytomegalovirus retinitis but with corticosteroids and cyclosporin—that will provide local treatment avoiding systemic side effects.[21 22]

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