The eye in systemic vasculitis

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Clin Med 2004;**4**:250–4

ABSTRACT – The term 'vasculitis' includes a wide range of disorders characterised by inflammation of the wall of blood vessels, sometimes with necrosis, leading to ischaemia of the affected organ. The exact pathogenesis of most of these vasculitides is not fully understood and although the presence of circulating auto-antibodies seems to be a common feature among them, each vasculitis has its unique pathogenesis and a predilection for vessels of a defined size. Systemic vasculitis may be associated with ocular complications which include scleritis, keratitis, uveitis and optic neuropathy. These can precede the symptoms/signs of the systemic disease and therefore their recognition may lead to detection of the underlying disorder. The eye may also be affected by the treatment required to control the systemic disease.

KEY WORDS: corticosteroids, cyclosporin, ischaemia, keratitis, mycophenolate mofetil, retinitis, scleritis, uveitis

Wegener's disease

Wegener's disease is a granulomatous systemic inflammatory disorder characterised by the triad of necrotising granulomatous inflammation of the upper and lower respiratory tract, vasculitis and glomerulonephritis. The aetiology of the disease remains unclear and different mechanisms have been implicated in its pathogenesis. The presence of c-ANCA has been used extensively as a diagnostic tool since van der Woude *et al* described the possible association between Wegener's disease and ANCA.[1]

Wegener's disease may present with ocular symptoms in 8–16% of patients, but the eye becomes involved in up to 40%.[2] Ocular involvement may be the result of focal vasculitis, granulomatous inflammation or ischaemia. Any tissue within the eye can be affected as well as the orbit and lacrimal system. Orbital involvement is one of the most characteristic forms of involvement. It tends to be bilateral and in the vast majority of cases is the result of the disease from the paranasal sinus or nasopharynx spreading into the orbit. Haynes *et al* reported radiological maxillary sinusitis in 86% of Wegener's patients with orbital involvement.[3] Less frequently, orbital disease occurs as primary orbital vasculitis.

Proptosis is the most common finding and in up to 17% of patients visual acuity is compromised as a result of compression of the optic nerve (Fig 1).[4]

The anterior segment is also a common site of ocular involvement.[5] Peripheral corneal inflammation and necrotising scleritis are among the commonest manifestations and may be the presenting sign of the disease. These inflammatory processes may progress and lead to ulceration and subsequent perforation (Fig 2). Involvement of the posterior segment is uncommon. It can manifest as an occlusive retinal vasculitis affecting either arteries or veins, retinitis or uveitis.[6] The optic nerve is the most frequently affected cranial nerve in Wegener's disease. Optic nerve involvement may resemble ischaemic optic neuropathy and can be associated with orbital disease or posterior scleritis or be secondary to vasculitis.[3]

Treatment

The clinical course and prognosis of Wegener's disease has changed dramatically since the introduction of immunosuppressive agents. As with management of the systemic disease, corticosteroids are the mainstay of therapy for the ocular inflammation which can either settle very quickly or be very refractory. Recurrent disease remains a problem and long-term therapy is often required to ensure that continuing ocular damage does not occur. Corticosteroids alone may fail to control the progressive course of the disease or only control the disease process at high

Key Points

- **Systemic vasculitis may be associated with ocular complications which include scleritis, keratitis, uveitis and optic neuropathy**
- **Ocular symptoms/signs may precede those of the systemic disease and therefore their recognition may lead to detection of the underlying disorder**
- **Despite advances in the use of immunosuppressive agents, recurrent disease remains a problem and long-term therapy is often required to ensure that continuing ocular damage does not occur**
- **The eye may also be affected by the treatment required to control the systemic disease including side effects of the drugs such as cataract but also opportunistic infections arising from severe systemic immunosuppression**

doses. Additional immunosuppressive agents are frequently used, most often cyclophosphamide, which has substantially lessened morbidity and increased the overall survival. When patients develop problems with cyclophosphamide, other drugs are being tried and cyclosporin and mycophenolate mofetil have been used.[7–9] In the longer term many patients may be switched to azathioprine.

Systemic lupus erythematosus

Systemic lupus erythematosus (SLE) is a chronic, systemic, immune mediated disease of unknown aetiology, in which presentation varies from cutaneous manifestations without systemic involvement to myocardial, pulmonary, neural or life-threatening renal complications. It may involve both anterior and posterior segments of the eye.

Keratoconjunctivitis sicca (KCS) is the most common ocular manifestation of SLE and occurs in approximately one-third of patients.[10] Occasionally SLE can present with scleritis and its activity often mirrors that of the systemic disease.[11] The prognosis is usually good as necrotising changes like the ones seen in Wegener's granulomatosis are rare.

Retinal involvement in the form of cotton wool spots (Fig 3), with or without venous engorgement and narrowing of the arterioles, is second in frequency after KCS.

These findings also parallel the activity of the systemic disease and are different from those found with hypertension which may complicate the ocular picture. Neovascularization may develop in cases where severe retinal vasculitis results in areas of retinal ischaemia. This is typically seen in aggressive systemic disease with associated central nervous system (CNS) involvement.[1] In addition to the small-vessel disease, some patients will suffer larger retinal vascular occlusions, eg retinal vein or arterial occlusions.[13]

Neuro-ophthalmic involvement in SLE can occur. Cranial nerves including the optic nerve and chiasm may be involved, usually as a result of an ischaemic process. Optic disc oedema can be secondary to central retinal vein occlusion, focal ischaemia or raised intracranial pressure, as well as systemic hypertension.[14]

Severe retinal vaso-occlusive disease and CNS involvement have been associated with the presence of antiphospholipid antibodies in the antiphospholipid syndrome.[15]

Treatment

The choice of immunosuppressive treatment depends on the organ involved and the severity of the lesions. Therapy for the

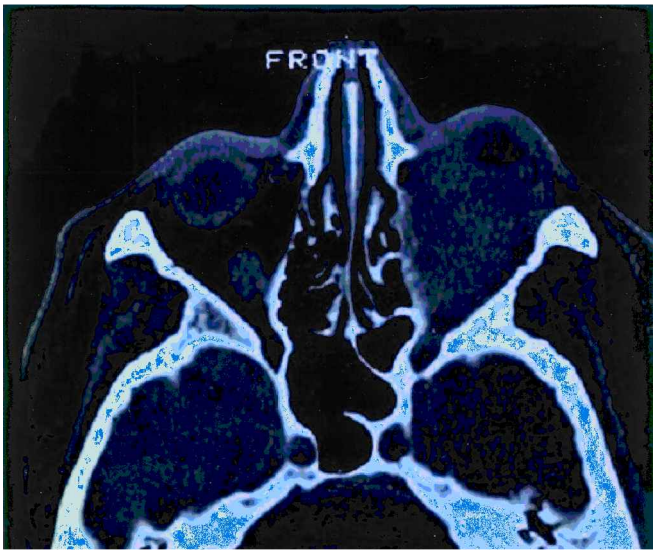

Fig 1. Sagital computed tomography scan of the orbits. Note the diffuse left orbital mass compressing the left optic nerve and proptosis in a patient with Wegener's granulomatosis.

Fig 2. Peripheral corneal inflammation and necrotising scleritis (black arrow) in a patient with Wegener's granulomatosis.

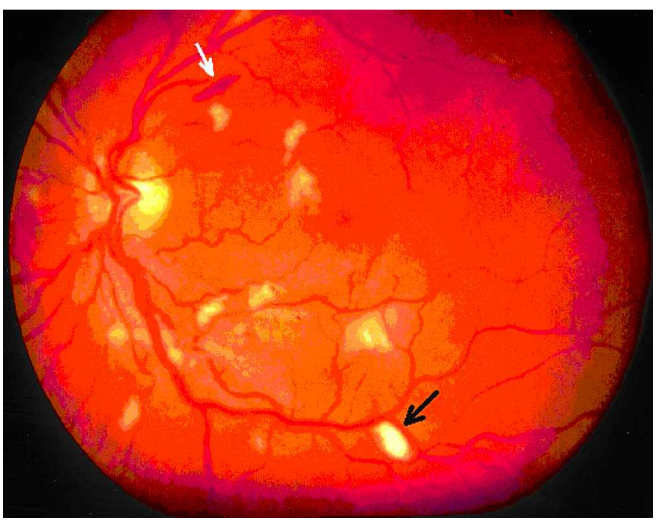

Fig 3. Multiple cotton wool spots (black arrow), retinal haemorrhage (white arrow) and vascular tortuosity in a patient with SLE retinopathy.

ocular manifestations as well as haematological, renal and CNS involvement has traditionally relied on systemic corticosteroids.

Rheumatoid arthritis

Rheumatoid arthritis (RA) is a symmetric, deforming polyarthritis which affects up to 2% of persons 60 years of age or older.[16] KCS is the commonest manifestation of Sjögren's syndrome associated with RA.[17] The ocular surface in KCS is poorly lubricated causing corneal epithelial changes.[18] Patients complain of a foreign body sensation, photophobia and decreased vision. On examination they may show conjunctival hyperaemia and conjunctival and corneal staining specially in the interpalpebral zone.

A small proportion of patients may develop severe corneal inflammation or even corneal melting and perforation indicative of a vasculitic stage of the underlying disease.[19]

Inflammation of the sclera can present as episcleritis or scleritis. Episcleritis, a more superficial ocular inflammation, usually presents with discomfort rather than pain and is rarely associated with ocular complications. On the other hand, scleritis, a deeper form of episcleral inflammation, is characterised by severe pain which characteristically radiates away from the eye and wakes the patient at night. There may be associated ocular complications, which can be sight-threatening.

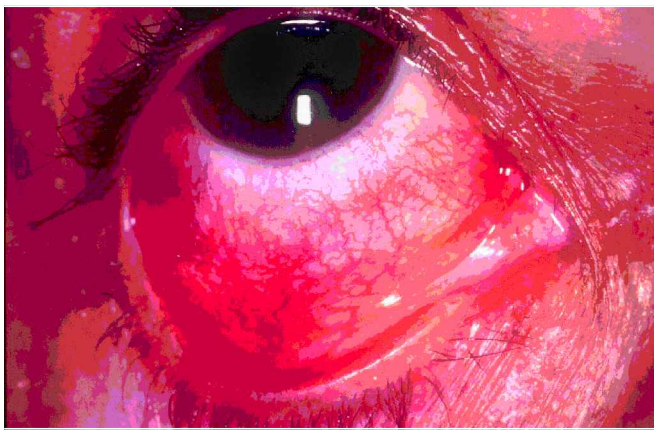

Fig 4. Diffuse anterior scleritis in a patient with rheumatoid arthritis.

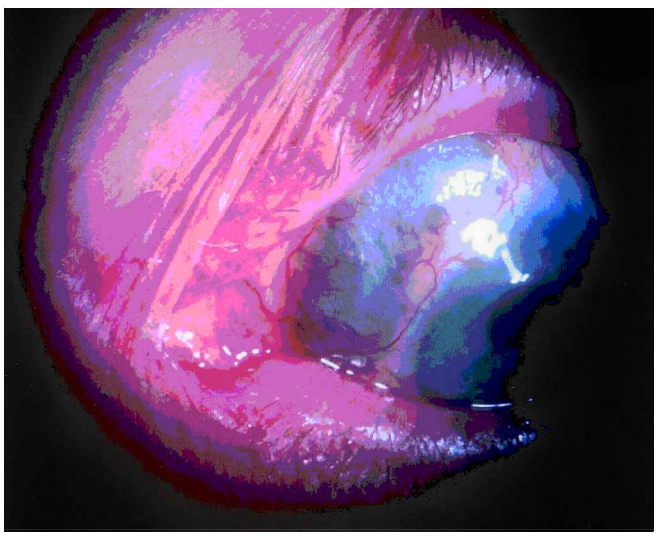

Fig 5. Quiet scleral necrosis in scleromalacia perforans. Note the scleral thinning with underlying bulging of the choroid, also known as staphyloma.

Scleritis may be classified as anterior, posterior and necrotising. Anterior scleritis can be subdivided into nodular and diffuse. Although all three forms can be seen in RA, the diffuse anterior type is the most commonly seen (Fig 4). Necrotising scleritis carries the worst visual and life prognoses.[20]

Scleromalacia perforans, much less common now, is an indolent, painless form of necrotising scleritis without inflammation in patients with long-standing RA, caused by arteriolar occlusive changes (Fig 5).

The incidence of uveitis is not increased in patients with RA, unless it is associated with scleritis. This is in contrast to juvenile idiopathic arthritis where uveitis is the predominant ocular disease.[21]

Treatment

Treatment for KCS consists of tear supplements, lacrimal punctal occlusion to increase the effectiveness of the tears that are produced, and occasionally tarsorrhaphy when the corneal epithelium has broken down and is not healing. Non-necrotising scleritis disease may respond to non-steroidal anti-inflammatory drugs, but necrotising disease must be treated with high dose corticosteroids very quickly as the integrity of the eye is compromised. Additional immunosuppressive therapy may be required with drugs such as cyclosporin,[22] azathioprine, mycophenolate,[23] methotrexate,[24] or less commonly cyclophosphamide if the corticosteroids are ineffective or too high a dose is required for disease control. Corneal perforation may require the application of glue or a tectonic graft to seal the hole in addition to the systemic medication.[25]

Behçet's disease

Behçet's disease (BD) is a multisystem disorder defined by clinical criteria which may include oral and genital ulcers and ocular inflammation.[26] Other manifestations include erythema nodosum, cutaneous thrombophlebitis, arthritis, intestinal ulcers, CNS involvement and major vessel thrombosis.

Ocular manifestations in BD are common and carry important implications for the patients as the ocular disease is associated with severe visual morbidity. The commonest ocular presentation of BD is uveitis with hypopyon formation (Fig 6). Although it may present as unilateral disease, both eyes are commonly affected with time. The main cause of visual loss in these patients is ischaemic vasculitis resulting in retinal and optic nerve damage (Fig 7).[27]

Other ocular manifestations of BD include scleritis, cataract and glaucoma, the last two being the result of severe recurrent inflammatory episodes.

Treatment

The natural history of BD has shown that over 70% of patients with ocular involvement will develop blindness, but with current immunosuppressive therapy which includes the use of steroids, cyclosporin, mycophenolate and others, the visual prognosis has improved.[23,28,29]

Takayasu's arteritis (pulseless disease)

Takayasu's arteritis is a granulomatous necrotising vasculitis that affects the aorta and its main branches, leading to obliteration. Ocular involvement is secondary to ocular ischaemia. Chun *et al* reported ocular symptoms in up to 44.9% of patients with Takayasu's arteritis, with amaurosis fugax (25.6%) as the most common. These symptoms are related to the narrowing of the carotid arteries, or transient retinal, choroidal or optic nerve ischaemia of embolic origin. Fundus examination in Takayasu's patients may also show retinal changes secondary to systemic hypertension (30.8%) or Takayasu's retinopathy (13.5%), which is a form of hypotensive retinopathy caused by decreased blood supply secondary to the vascular abnormalities at the aortic arch. Patients with involvement of the descending aorta and retinal artery with sparing of the carotid arteries had hypertensive retinopathy, whereas those with carotid artery or aortic arch involvement showed changes secondary to Takayasu's retinopathy.[30]

The main ocular findings of Takayasu's retinopathy are generalised retinal vasodilation and microaneurysm formation. More advanced disease will lead to arteriovenous anastomoses, peripheral retinal non-perfusion and eventually sight-threatening complications such as neovascular glaucoma, vitreous haemorrhage, retinal detachment, anterior ischaemic optic neuropathy and optic nerve atrophy.[31]

Polyarteritis nodosa (PAN)

PAN is a non-granulomatous necrotising vasculitis affecting medium size and small vessels. Ocular involvement occurs in 10–20% of patients.[32] Retinopathy is one of the most commonly seen ocular complications, with retinal vascular occlusions, oedema, cotton wool spots and retinal haemorrhages. These findings are secondary to hypertensive retinopathy, especially in patients with renal disease, or from primary retinal vasculitis. Papilloedema with subsequent optic disc atrophy and extraocular muscle dysfunction secondary to cranial nerve palsies have also been reported.[33,34]

Involvement of the anterior segment is not uncommon, with peripheral corneal ulceration and scleritis.[35]

Kawasaki disease

Kawasaki disease is an acute exanthematous illness of unknown origin with multisystemic involvement. It occurs almost exclusively in children under five years of age. Bilateral conjunctival injection is part of the diagnostic criteria together with fever, oropharyngeal changes, peripheral extremity changes, erythematous truncal rash and cervical lymphoadenopathy. Vasodilatation of the conjunctival vessels with little or no inflammation and no purulent discharge occurs in more than 90% of children with Kawasaki's disease. It usually appears 2 to 4 days after the onset of symptoms. Two-thirds of patients have evidence of an acute non-granulomatous iridocyclitis but no posterior synechiae.[36] Superficial punctate keratitis, vitreous opacities and papilloedema are rare. These ocular manifesta-

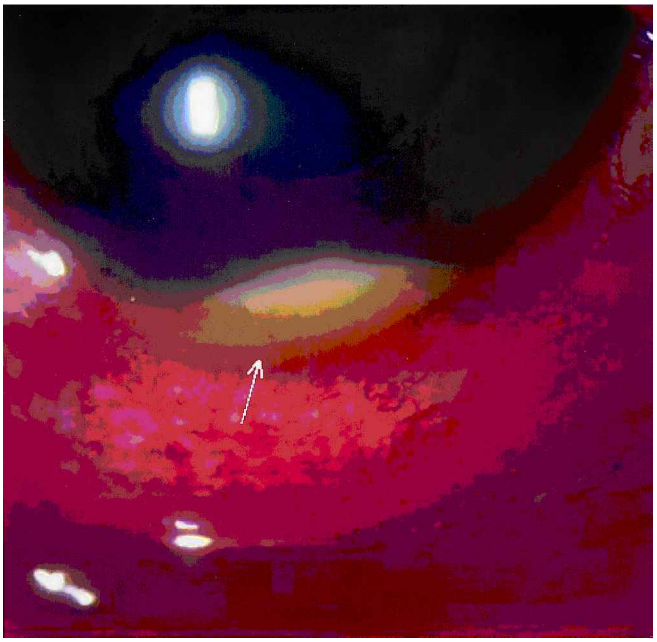

Fig 6. Anterior uveitis with hypopyon (white arrow) formation in a patient with Behçet's disease.

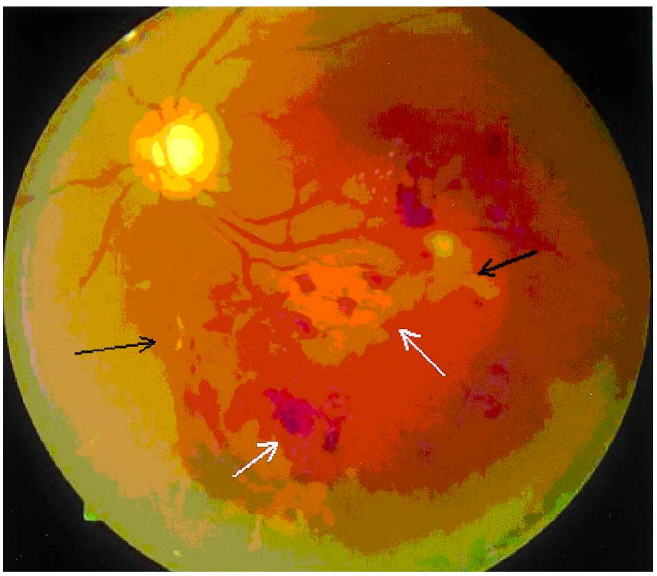

Fig 7. Acute occlusive retinal vasculitis in a patient with Behcet's disease. Note the retinal haemorrhages and oedema (white arrows) with closure of the retinal veins (black arrows).

tions tend to be bilateral and usually resolve completely without sequelae.[37]

Churg-Strauss syndrome

Churg-Strauss syndrome is also known as allergic granulomatosis and angiitis. It was first described in 1951 by Churg and Strauss in a series of patients with asthma, fever, eosinophilia and necrotising vasculitis.[38] Although a wide range of ocular lesions have been reported, the eye is rarely involved. Lesions include episcleritis, peripheral ulcerative keratitis, uveitis, ischaemic optic neuropathy and cranial nerve palsies.[39]

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