Ophthalmic manifestations of giant cell arteritis

This article reviews the ophthalmic manifestations of giant cell arteritis. An overview of giant cell arteritis as a disease spectrum is presented with special emphasis on the ophthalmic involvement.

Giant cell arteritis is a systemic inflammatory vasculitis of unknown aetiology that affects medium- and large-sized arteries resulting in systemic, ophthalmic and neurological complications (Ganchi and Dutton, 1997; Ghosh, 2002). Visual loss can occur in up to 30% of patients so the condition must be treated as a true neuro-ophthalmic emergency (Danesh-Meyer et al, 2005).

Epidemiology

The majority of epidemiological data on giant cell arteritis come from Scandinavian studies where an annual incidence of 15–35 per 100 000 people older than 50 years has been reported (Watts and Scott, 2002). A retrospective study from north-west Spain showed the average incidence in those over 50 years was 10.24 per 100 000 (Gonzalez-Gay et al, 2001). Age is the most important risk factor. The disease is seen in those older than 50 years with an increasing incidence with age.

Liu et al (2001) reported a retrospective study at an ophthalmology unit in southern California. Of the 121 patients undergoing temporal artery biopsy, nineteen of 66 (29%) white patients had a positive biopsy result as did one of nine Asian patients (11.0%), none of 40 Hispanic patients (0%), and none of six (0%) African-American patients. They concluded that non-white patients might be protected from the disease although this needs to be investigated further.

Women are 2–4 times more likely to have giant cell arteritis than men (Machado et al, 1988). The 1990 American College of Rheumatology criteria for diagnosis of giant cell arteritis are most widely used to aid diagnosis (Hunder et al, 1990).

Incidence of visual manifestations

In a prospective study of 174 patients (147 biopsy proven), Liozon et al (2001) found that visual ischaemic manifestations occurred in 48 (28%) patients including permanent visual loss in 23 (13%) patients. Nesher et al (2001) reported a prospective study of 31 patients and found permanent visual loss in five (16%) and amaurosis fugax in one (3.3%) patient.

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Pathophysiology

Giant cell arteritis can involve almost any artery of the body and can occasionally affect veins as well. Histologically, an inflammatory infiltrate of mononuclear cells is seen involving the entire vessel wall. Giant cells are present, but their absence does not exclude giant cell arteritis. Fragmentation of the internal elastic lamina is characteristic.

The involvement is mostly segmental where patches of normal vessel alternate with inflamed segments. It has long been felt that vessel susceptibility to giant cell arteritis is determined by the presence and quantity of supporting internal elastic lamina within the vessel wall (O'Brien and Regan, 1992). This would explain why the intracranial cerebral vasculature, by virtue of a lack of internal elastic lamina, is not primarily affected in giant cell arteritis. In contrast, the extracranial vertebral arteries, particularly the superficial temporal, ophthalmic and posterior ciliary arteries, are most commonly affected. Kaiser et al (1998) analysed temporal artery biopsy specimens from patients with giant cell arteritis for the presence of intimal hyperplasia. They found that the platelet-derived growth factors A and B are widely expressed in inflamed arteries. These are produced by CD68+ macrophages, smooth muscle cells and multinucleated giant cells at the media-intima junction. These cells also frequently coproduce matrix metalloproteinase 2. The resultant intimal hyperplasia leads to the ischaemic complications of giant cell arteritis (*Figure 1*).

The role of cytokine release by inflamed vessels in giant cell arteritis has been debated. A review by Martinez-Taboada et al (2008) concluded that giant cell arteritis is characterized by hyper-production of interleukin-6. Further studies are needed to clearly establish the role of circulating cytokines.

Although the exact aetiology remains unknown, various causes have been postulated. As discussed above, the presence of pro-inflammatory cytokines and the granulomatous histopathology of giant cell arteritis suggest an autoimmune aetiology. Álvarez-Lafuente et al (2005) conducted polymerase chain reaction analysis of temporal

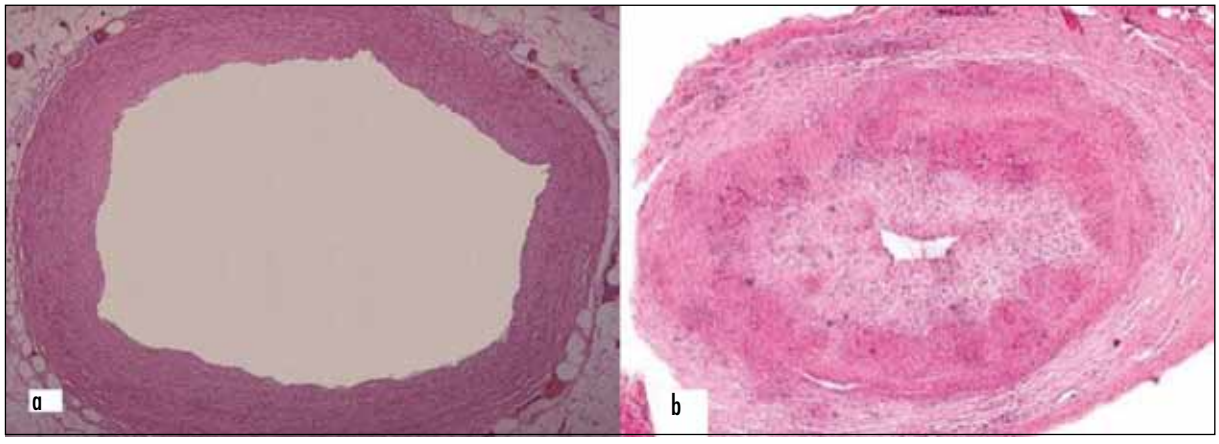


Figure 1. a. Normal temporal artery with non-thickened walls and patent vessel lumen. b. Temporal artery with giant cell arteritis. Note the thickened intima and media with inflammatory cells.

artery biopsies and observed that parvovirus B19 may have a role in the pathogenesis of giant cell arteritis, particularly in those patients with high viral load. No evidence was found for involvement of varicella zoster virus or human herpesvirus-6. Conflicting data exists regarding the role of *Chlamydia pneumoniae* and cytomegalovirus. Some authors found a strong correlation (Rimenti et al, 2000), whereas others failed to detect the pathogens (Cankovic and Zarbo, 2006; Njau et al, 2009). Some investigators have also reported evidence of a genetic or hereditary predisposition (Liozon et al, 2009).

Systemic symptoms and signs

Giant cell arteritis can present with prodromal symptoms of anorexia, malaise, fever, night sweats and weight loss. These symptoms can be sudden in onset but may have been present for many weeks. Most characteristic is a new onset localized headache mostly in the temporal or occipital region. This may be associated with scalp tenderness. Patients often describe tenderness on gentle pressure to the scalp such as during combing hair. Patients may also have pulseless and palpable, hard, cord-like temporal arteries.

Jaw claudication is almost pathognomic and is secondary to ischaemia of the masseter muscle leading to pain on speaking and chewing (Unwin et al, 2006). Other symptoms include tongue claudication and palatal pain, toothache, earache and facial pain. Extracranial involvement of common, external and internal carotid arteries can cause bruits in the neck. Bhatti (2001) and Dudenhoefer et al (1998) reported cases of scalp necrosis associated with giant cell arteritis.

There is also a considerably increased relative risk, up to 17 times, of developing thoracic aortic aneurysm and aortic dissection (Neunninghoff et al, 2003; Gonzalez-Gay et al, 2004). Evans et al (1995) reported aortic aneurysms occurring in 15% of patients at a median of 6 years after the giant cell arteritis initially was diagnosed. Two thirds were thoracic aortic aneurysms, with the majority in the ascending aorta. Almost 33% developed symptomatic aortic regurgitation, and 50% of those with thoracic aortic aneurysms died suddenly from aortic dissection.

Giant cell arteritis can also cause coronary arteritis and myocardial infarction but it is not known how often this occurs (Bahlas et al, 1998). Pericarditis has also been described in several case reports (Guillaume et al, 1991; Stanley et al, 1991). Renal failure and brainstem stroke may also ensue.

Giant cell arteritis and polymyalgia rheumatica are thought to be closely related disorders that can frequently occur together (Salvarani et al, 2008). It has been suggested that they might even be different stages of the same disease spectrum. Polymyalgia rheumatica is characterized by pain and stiffness in proximal muscle groups (typically the shoulders). It is typically worse in the morning and after exertion and is characterized by elevated erythrocyte sedimentation rate responding rapidly to low-dose corticosteroids (prednisolone 10 mg/day).

Diaz et al (2005) found that clinical symptoms of giant cell arteritis correlate strongly with histopathological features and biochemical markers which highlights the importance of a thorough history and examination.

Ophthalmic symptoms and signs

Visual loss with progression to permanent visual impairment is one of the most significant morbidities associated with giant cell arteritis (Kupersmith et al, 2001). Visual recovery is uncommon. In a multicentre prospective case series of 34 biopsy-proven patients with visual loss, Danesh-Meyer et al (2005) found that in cases where visual acuity does improve, corresponding improvements in colour vision and visual fields might not be seen. They also found that visual deterioration occurred in approximately 27% of eyes despite high-dose intravenous methylprednisolone with the greatest risk in the first 6 days.

The most common cause of visual loss is arteritic anterior ischaemic optic neuropathy caused by involvement of the posterior ciliary arteries leading to ischaemia of the

optic nerve head. Patients will present with sudden, painless visual loss with systemic symptoms of giant cell arteritis. Critical signs include an afferent pupillary defect, counting fingers or worse vision, a pale swollen optic disc with flame-shaped haemorrhages leading eventually to optic atrophy and cupping of the optic disc. Visual field defects may also be present (typically inferior altitudinal or central). Posterior arteritic ischaemic optic neuropathy is much less common and is caused by ischaemia of the retrolaminar portion of the optic nerve which is supplied by the surrounding pial capillary plexus. Anterior ischaemic optic neuropathy may be preceded by transient ischaemic attacks (amaurosis fugax) and visual obscurations (Nesher, 2000). Combined anterior ischaemic optic neuropathy and cilioretinal artery occlusion have been reported (Galasso and Jay, 2004). Central retinal artery occlusions may also be seen (Connolly et al, 2000). Rarely, ocular ischaemic syndrome has been associated with giant cell arteritis (Casson et al, 2001). Cotton wool spots are seen secondary to platelet microembolization from the partially thrombosed ophthalmic or central retinal artery.

Nesher et al (2001) found that complex visual hallucinations preceded visual loss in giant cell arteritis and could be a harbinger of permanent visual loss. Diplopia secondary to ischaemia of the cranial nerves, ptosis (Killer et al, 2000), internuclear ophthalmoplegia (Ahmad and Zaman, 1999) and tonic pupils (Foroozan et al, 2003) have also been reported.

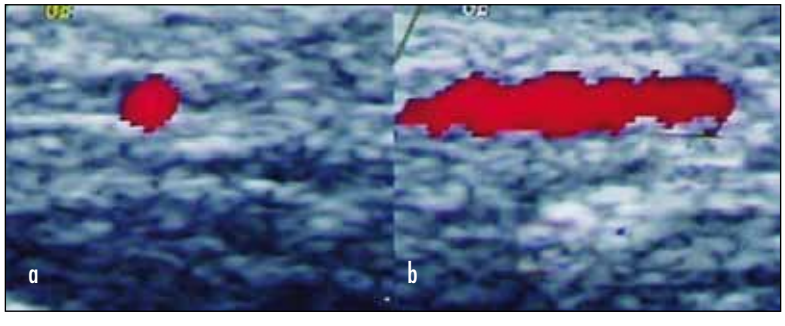
Diagnosis

American College of Rheumatology criteria

Based on the 1990 American College of Rheumatology criteria for diagnosis of giant cell arteritis, at least three of the following five items must be present (sensitivity 93.5%, specificity 91.2%) (Hunder et al, 1990):

1. Age of onset older than 50 years
2. New-onset headache or localized head pain
3. Temporal artery tenderness to palpation or reduced pulsation
4. Erythrocyte sedimentation rate greater than 50 mm/h
5. Abnormal arterial biopsy (necrotizing vasculitis with granulomatous proliferation and infiltration).

Figure 2. Normal common temporal artery. Demonstration of the left superficial temporal artery trunk by colour duplex sonography in a healthy person. a. Transverse and (b) longitudinal planes.



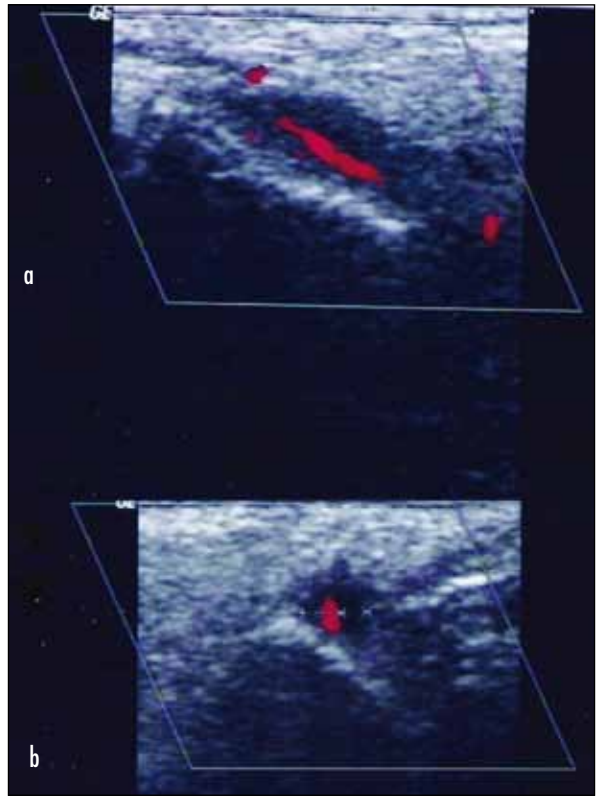
Inflammatory markers

These include erythrocyte sedimentation rate, C-reactive protein and plasma viscosity. Erythrocyte sedimentation rate and C-reactive protein are commonly elevated, but normal results do not conclusively rule out giant cell arteritis (Poole et al, 2003; Parikh et al, 2006). More recently, erythrocyte sedimentation rate has been replaced by plasma viscosity as the test of choice for laboratories. Brittain et al (1991) found both had similar false negative rates (13.3%) and concluded that clinical judgment based on careful assessment of all available symptoms and signs must remain the foundation of diagnosis. Elevated platelet counts have also been described as an association (Foroozan et al, 2002).

Carotid duplex ultrasonography

Carotid duplex ultrasonography of the temporal arteries has been advocated as a novel technique. The diagnostic feature is vessel wall oedema which is seen as a dark ring around the vessel (halo sign) (*Figures 2* and *3*). A meta-analysis by Karassa et al (2005) concluded that this had a weighted sensitivity and specificity of 69% and 82% respectively compared with biopsy and 55% and 94% respectively compared with American College of Rheumatology criteria. The same diagnostic feature can also help in temporal artery biopsies by identifying skip lesions. Thus ultrasonography may be helpful in diagnosing giant cell arteritis, but cautious interpretation of

Figure 3. Halo sign in colour duplex sonography examination in a patient with giant cell arteritis. Hypoechoic area around the temporal artery trunk in (a) longitudinal and (b) transverse views.



the test results based on clinical presentation and pretest probability of the disease is imperative. At present this is not widely adopted as routine practice.

Temporal artery biopsy

A temporal artery biopsy remains the gold standard for diagnosing giant cell arteritis (Myklebust and Gran, 1996). This does not need to be done as an emergency, but ideally should be done within 4 weeks of starting steroids as these may suppress histological evidence of active arteritis (Narváez et al, 2007). However, steroid treatment should not be withheld pending the biopsy. In patients with ocular involvement, a biopsy should be taken from the ipsilateral side. Ideally a 2.5 cm segment of the artery should be taken to avoid missing skip lesions. A positive biopsy is diagnostic (100% specificity) and the histopathological changes often correlate with clinical features of severity. However, the sensitivity of temporal artery biopsy is relatively low at 15–40% (Roth et al, 1984). A false-negative temporal artery biopsy may be caused by too short a specimen, the presence of skip lesions, sectioning techniques or steroid therapy before biopsy. Thus, a normal temporal artery biopsy does not exclude the disease, and many patients are diagnosed with giant cell arteritis despite a normal temporal artery biopsy, based on high clinical suspicion.

Some authors have advocated either bilateral simultaneous or sequential temporal artery biopsies (if the ipsilateral temporal artery biopsy is negative with high clinical suspicion) (Boyev et al, 1999). There is, however, a low yield of extra information from a second temporal artery biopsy in patients with suspected giant cell arteritis. This suggests that patients who present to the ophthalmologist with possible giant cell arteritis will, in most cases, have similar histology of both temporal artery biopsies if the specimens are adequate (Danesh-Meyer et al, 2000). In reality, given the severe complications associated with giant cell arteritis, most clinicians will make their own judgement regarding the justification for a second temporal artery biopsy.

Arranging a temporal artery biopsy involves a multidisciplinary approach. Different units across the NHS have differing guidelines as to who should perform a temporal artery biopsy and it is important to be aware of local guidelines and make an appropriate referral. Specialities that can undertake a temporal artery biopsy include ophthalmology, vascular surgery, general surgery, maxillofacial surgery and neurosurgery (Galloway et al, 2002).

Treatment

Patients with giant cell arteritis present to different clinical teams based on initial symptoms. In the absence of visual loss they will present to accident and emergency or to the acute medicine team. Patients with visual symptoms will usually present to eye casualty.

Birkhead et al (1975) showed that prompt treatment with corticosteroids could prevent visual loss, but the treatment regimen of choice remains contentious. Chan et al (2001) conducted a two-centre retrospective study to review the effects of intravenous *vs* oral steroids in giant cell arteritis. They concluded that prompt treatment of giant cell arteritis with steroids leads to improvement of visual acuity in a significant number of cases, with intravenous steroids offering a greater prospect of improvement than oral steroids. However, prospective trials comparing intravenous with oral steroids are needed to validate these findings. In the literature, dose recommendations for intravenous methylprednisolone vary from a single 500 mg dose to 1 g daily for durations of between 1 and 5 days (Paice, 1989; Hunder, 1990) followed by oral treatment. Alternatively, high doses of oral prednisolone (1–2 mg/kg/day) may be given for 1 month. They can then be tapered gradually based on serial inflammatory marker monitoring. Treatment may need to be continued for 1–2 years.

More recently, the use of methotrexate or infliximab has been studied in steroid-resistant cases or where steroids are contraindicated (Pipitone et al, 2005). Nesher et al (2004) reported that the addition of low-dose acetylsalicylic acid to steroid treatment decreased the incidence of cerebrovascular accidents and visual loss in a retrospective analysis of 175 patients diagnosed with giant cell arteritis between 1980 and 2000.

Conclusions

Visual loss is the most dreaded complication of giant cell arteritis. Prompt diagnosis and treatment with high dose steroids can prevent this and provide the best chance of visual recovery. Close collaboration between ophthalmology and acute medical teams is important for the prompt initiation of treatment. **BJHM**

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Conflict of interest: none.

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KEY POINTS

- Visual symptoms are common with giant cell arteritis and can lead to visual deterioration and loss.
- Prompt treatment with high-dose steroids can prevent visual complications.
- A multidisciplinary approach is required to promptly diagnose giant cell arteritis and initiate appropriate treatment.

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