Investigation and management of giant cell arteritis

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Early recognition of the symptoms of giant cell arteritis (GCA), followed by urgent referral and treatment are important in order to prevent possible sight loss. This article discusses the clinical presentation of GCA, the investigations needed to aid diagnosis, and recommended management.

Giant cell arteritis (GCA) is the most common form of vasculitis. Affecting large and medium-sized vessels, it is a chronic granulomatous vasculitis that commonly affects the cranial branch vessels that arise from the aortic arch. Worryingly, up to one in five patients will suffer the devastating consequences of sight loss.1

The treatment of GCA has historically relied upon corticosteroids. This has resulted in almost half of patients suffering from corticosteroid-related adverse effects (the most common being cataracts and bone loss).2 Horton et al.3 first described the condition in 1890 as “arteritis of the aged” because of its predilection for the elderly. Historically, and inaccurately, it was sometimes referred to as “arteritis temporalis” (temporal arteritis). We no longer use this term because we now know that GCA does not just affect the temporal arteries and can frequently cause large vessel vasculitis (aortitis).

Epidemiology and aetiology

The incidence of GCA in the UK is reported to be 2.2 per 10,000 patient years.4 It mainly affects white people and almost exclusively those over the age of 50 years. Two to six times as many women are affected as men and the incidence increases with age. GCA is commonly associated with the condition polymyalgia rheumatica (PMR). A fifth of PMR patients will actually have ‘silent’ biopsy-proven GCA,5 and about half of GCA patients will have PMR symptoms.6 Epidemiological studies have found an increase in incidence with latitude in the Northern Hemisphere, with the highest incidence in Scandinavian countries.7 The incidence of GCA is much lower in southern European and Mediterranean countries.8

The aetiology is unknown but seasonal variation is known to occur. Environmental causes such as infections have been implicated. Fluctuations in the incidence of GCA/PMR have supported an association with Mycoplasma pneumoniae, parvovirus B19, and Chlamydia pneumoniae.9
Clinical presentation
The following symptoms in a patient aged over 50 years should lead one to consider GCA as a possible diagnosis:1
• Abrupt-onset headache – usually unilateral in the temporal area
• Scalp tenderness – difficulty wearing glasses/hats or combing hair
• Jaw and tongue claudication – pain associated with use, eg chewing/eating, relieved with rest
• Visual symptoms – including diplopia, amaurosis fugax
• Constitutional symptoms – fever, malaise and weight loss
• Polymyalgic (PMR) symptoms – proximal myalgia, neck, shoulder and hip stiffness, eg difficulty getting out of chairs, dressing or tying shoe laces
• Limb claudication – muscle pain/weakness associated particularly with use of arms, eg difficulty with activities such as hanging up the washing or vacuuming.

Headache
The headache associated with GCA is usually temporal and unilateral, it does not tend to respond to analgesia and is present in approximately 75% of patients. It is generally a constant headache located in the temporal area. Intermittent or variable headaches are less commonly described.

Specific symptoms associated with GCA include jaw claudication, which arises from ischaemia of the chewing muscles. Similar processes can occur that can give rise to swallowing problems and tongue pain, albeit less commonly. Scalp tenderness is specific to GCA; patients might not be able to tolerate hair being brushed, wearing hats or glasses resting on their heads. Changes that can be detected along the temporal artery, including tenderness on palpation, knotty swellings and absence of pulse, are signs specific for GCA.10

Large vessel involvement
The majority of GCA patients will have large vessel involvement, as evidenced by uptake on FDG-PET imaging.11 This explains why GCA patients have a much larger incidence of thoracic (17 times more common) and aortic (twice as common) aneurysms. Aneurysms affect one-fifth of GCA patients and are usually identified about six years after initial diagnosis.10 Aortic involvement increases the overall risk of mortality. Large vessel involvement can be detected clinically by reduced or absent peripheral pulses. There can be difficulty in getting blood pressure readings. Symptoms often described are limb claudication (particularly in the arms), pain/weakness associated with activity, eg difficulty with housework, which are relieved with rest.

Eye involvement
Eye involvement occurs in up to 70% of patients. If there is eye involvement and a patient is left untreated, about 60% will go blind in the contralateral eye. The most frequent eye complication is anterior ischaemic optic neuropathy. This occurs secondary to inflammatory occlusion of the posterior ciliary arteries. It presents as sudden painless loss of vision (or visual field). Although rarer, occlusion of the retinal central artery can also lead to sudden painless loss of vision.10

Diplopia (double vision) can occur when there is ischaemia affecting the ocular muscles, nerves or brainstem. Precursors to sight loss include amaurosis fugax (transient blindness described as being like a curtain descending across the vision) and cotton-wool spots on examination. Double vision can improve with treatment but generally loss of vision is irreversible.

Poor prognostic features of neuro-ophthalmic complications include jaw claudication, temporal artery abnormalities and diplopia.1

Examination and investigations
The following should be looked for in patients with suspected GCA:
• Temporal artery may be tender, thickened, beaded. It may be difficult to feel the pulse
• They may complain of scalp tenderness
• Evidence of large vessel vasculitis should be sought – delayed or absent pulses in upper limbs, subclavian or carotid bruits, blood pressure asymmetry
• An ophthalmological exam should be carried out – look for transient or permanent visual loss, visual field defect, relative afferent papillary defect, anterior ischaemic optic neuritis, central retinal artery occlusion
• Look for evidence of upper cranial nerve palsies.1

The British Society for Rheumatology (BSR) 2010 guidelines1 advise that if GCA is suspected, the following investigations should be arranged immediately:
• Blood tests: full blood count, urea and electrolytes, liver function tests, C-reactive Protein (CRP) and erythrocyte sedimentation rate (ESR). There is often evidence of an acute-phase response on blood tests, ie raised ESR, CRP platelets, abnormal liver chemistry (particularly alkaline phosphatase)
• Chest X-ray
• Urinalysis.
Raised markers of inflammation (ESR, CRP) would be expected in GCA. Baseline (pre-treatment) markers of inflammation are also useful to assess response to treatment. It is important to consider other causes of raised inflammatory markers including infection (particularly respiratory and urinary infection). A chest X-ray can sometimes pick up an enlarged aorta, which could be a sign of aortic involvement or aneurysm. A raised serum calcium could indicate cancer or myeloma.

Initial management
If GCA is suspected, urgent referral to a specialist for immediate review is advised. This should be a rheumatologist if there are no visual symptoms, and/or an ophthalmologist if there are visual symptoms.

Prompt initiation of corticosteroid treatment by the treating doctor is advised:
- For uncomplicated GCA (no jaw claudication or visual symptoms): prednisolone 40–60mg daily
- Evolving visual loss or amaurosis fugax (complicated GCA): methylprednisolone 500mg–1g IV for three days before oral corticosteroids
- Established visual loss: prednisolone 60mg daily to protect the contralateral eye.

Treatment should not be delayed while awaiting results of blood tests or temporal artery biopsy. If there is a clinical suspicion for GCA, corticosteroid treatment should be initiated immediately.

Diagnosis
There are a number of investigations that can also be carried out to help confirm diagnosis, as outlined below.

Temporal artery biopsy
Temporal artery biopsy (TAB) remains the gold standard for diagnosis (see Figure 1). TAB is a day case procedure carried out with a local anaesthetic. However, it remains an invasive test that is not always readily available. It is also operator dependent. The likelihood of a positive result decreases after two weeks of corticosteroid therapy. (Treatment should not be withheld for this reason.) A negative result does not rule out the condition (10–20% of GCA cases will be biopsy negative). GCA biopsy is characterised by inflammatory infiltration of the arterial wall by lymphocytes, macrophages and giant cells (in about 50% of cases; see Figure 2).

Temporal artery ultrasound
Colour-coded duplex sonography can examine temporal, extracranial, occipital and subclavian arteries. Inflammatory oedema of the vascular wall will be shown as hypoechoic wall thickening – so-called ‘halo sign’ (see Figure 3). With experienced sonographers, an ultrasound study has a sensitivity of 85% and specificity of >90%. Ultrasound has been shown to be more cost effective than TAB.

Positron emission tomography
Positron emission tomography (PET) is an imaging modality being utilised more and more for the investigation of pyrexia of unknown origin. PET uses radioactive metabolites to visualise metabolic processes. Spatial resolution is limited with PET, so visualisation can only be determined in the aorta and larger vessels (see Figures 4–6). In patients with GCA, 83% will show activity in the aorta and great arteries on PET. Temporal arteries are unlikely to be seen with PET. The European League Against Rheumatism (EULAR) recommendations do not advise the use of PET to visualise the cranial vessels. However, newer PET scanners with improved spatial resolution may be able to visualise the temporal arteries better in the future.

High-resolution magnetic resonance imaging
EULAR recommends magnetic resonance imaging (MRI) or ultrasound for imaging of cranial vessels. High-resolution MRI (fat suppression, T1 weighted) allows detailed imaging of the walls and lumen of superficial cranial arteries. MR angiography at the same time allows imaging of large vessels of aorta and supra-
Aorta. Mural inflammation changes rapidly disappear after corticosteroid initiation.\textsuperscript{10}

\textbf{American College of Rheumatology classification criteria}

The 1990 American College of Rheumatology criteria for GCA\textsuperscript{14} are classification rather than diagnostic criteria, but can be a helpful tool to assess someone’s likelihood of having GCA. To be classified as GCA requires more than three of the following:

- Age >50 years
- New onset of localised headache
- Abnormality of temporal artery (temporal artery tenderness, reduced pulsation)
- Raised ESR >50mm/first hour
- Abnormal arterial biopsy (vasculitis with predominantly mononuclear cell infiltration, granulomatous inflammation or evidence of giant cells).

\textbf{Ongoing management}

Ongoing management of CGA should be as per the BSR guidelines.\textsuperscript{1} This is a suggested corticosteroid tapering regimen:

- Start with prednisolone 40–60mg daily continued until symptoms and laboratory abnormalities resolve (at least three to four weeks)
- Then reduce the dose by 10mg every two weeks to 20mg daily
- Then further reduce the dose by 2.5mg every two to four weeks to 10mg daily
- Then reduce by 1mg every one to two months, provided there is no relapse.

This is a suggested dosing regimen only. Other factors can influence a corticosteroid reduction, including co-morbidities, patient wishes and adverse events. Corticosteroids are generally reduced in the absence of clinical features of active disease and when there is normalisation of inflammatory markers, unless there are alternative reasons for raised inflammatory markers (e.g., age, gender, smoking history, cancer, raised body mass index). Relapse is common and almost half of patients will require an increase in corticosteroids despite an initial good response.\textsuperscript{8} Some patients will end up with lifelong corticosteroid treatment.

\textbf{Aspirin}

Aspirin use is controversial;\textsuperscript{15} however, it remains in the recommendations\textsuperscript{1,13} where there is no contraindication. Some retrospective analyses have found that aspirin is protective against cerebrovascular and cardiovascular events.\textsuperscript{16} It is used because of its antiplatelet effects and it may also have disease-modifying effects through suppression of interferon (IFN) gamma.

\textbf{Proton pump inhibitors}

A proton pump inhibitor can be co-prescribed with corticosteroid therapy to protect against gastric irritation, especially in the elderly and those also on aspirin.

\textbf{Bone protection}

In 2017, the National Osteoporosis Guideline Group produced new guidelines\textsuperscript{17} for patients on corticosteroid therapy. These guidelines provide the following recommendations:

- Women and men aged >70 years with a previous fragility fracture or taking high doses of corticosteroids (>7.5mg daily prednisolone) should be considered for bone-protective therapy
- In other individuals, fracture probability should be estimated using the FRAX tool with adjustment for corticosteroid dose
- Bone-protective therapy should be started at the onset of corticosteroid therapy in individuals at high risk of fracture, e.g., those >65 years of age and those with previous history of fragility fracture
- The bisphosphonates alendronate and risendronate are first-line treatment options. Where these are contraindicated or not tolerated, zoledronic acid or teriparatide are alternatives
- Bone-protective therapy may be appropriate in some premenopausal women and younger men, particularly individuals with a previous history of fracture or receiving high doses of corticosteroids.

\textbf{Management of relapse}

All patients with suspected relapse should be referred to or have their treatment discussed with a specialist. A rise in inflammatory markers (ESR/CRP) is usually seen in relapse, but inflammatory markers can remain normal. If there is recurrence of headache, the patient should go back to the previous higher dose of corticosteroid. Jaw claudication requires prednisolone 60mg daily. Eye symptoms require prednisolone 60mg daily orally or methylprednisolone 1g IV stat and immediate discussion with an ophthalmologist.

\textbf{Recurrent relapse}

Within two years, about 30–50% of patients will have suffered a relapse, despite an initial good response to therapy. This can warrant consideration of secondary agents. Early introduction of methotrexate (or other agents such as azathioprine for those with contraindications or who are intolerant to methotrexate) should be considered in patients with recurrent relapse or failure. Methotrexate (7.5–15mg once a week) has been shown in trials to reduce relapse rate and overall corticosteroid exposure.\textsuperscript{18}
Tocilizumab

Tocilizumab is an interleukin-6 (IL-6)-receptor inhibitor. NICE (TA518) has approved tocilizumab for use in relapsing or refractory GCA. The Giant Cell Arteritis Actemra (GiACTA) trial revealed that patients treated with tocilizumab plus corticosteroids had increased rates of sustained remission compared with those treated with corticosteroids alone. Furthermore, tocilizumab treatment reduced steroid-induced adverse effects.

When used with a tapering course of corticosteroids (and when used alone after corticosteroids), tocilizumab is recommended by NICE as an option for treating GCA in adults, only if: they have relapsing or refractory disease and they have not already had tocilizumab; it is stopped after one year of uninterrupted treatment at most; and the company provides it with the discount agreed in the patient access scheme.

Tocilizumab is a potent suppressor of IL-6, which is important for the production of CRP. Therefore, patients on tocilizumab may not produce a biochemical inflammatory response in the setting of infection/inflammation, ie they may have normal inflammatory markers. Caution should be taken as there is a risk of gastrointestinal perforation, particularly in patients with a history of diverticulitis.

Conclusion

Early recognition of the symptoms of GCA, urgent referral and initiation of treatment are needed in primary care to prevent the devastating and often irreversible consequent symptom of blindness. The advent of PET/CT scanning has led to an increased understanding of this condition and, in particular, large vessel vasculitis (often in the absence of temporal/cranial involvement). Historically, we have had very little to offer patients with GCA except increased doses of corticosteroids. However, corticosteroid exposure carries with it a burden of side-effects for the patient. NICE has recognised the need to reduce this and recommends adjunctive therapy for certain patients with GCA.

References


Declaration of interests

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