Giant cell (temporal) arteritis is a large vessel vasculitis that characteristically involves the cranial arteries in people over the age of 50 years. Timely recognition and immediate treatment with corticosteroids aims to prevent blindness and other complications. Close monitoring with specialist input helps minimise disease morbidity and treatment-related complications.

**Giant cell arteritis (GCA)**, also known as temporal arteritis, is a chronic medium to large vessel vasculitis that occurs in people over the age of 50 years. It commonly involves the cranial arteries, and may cause acute irreversible visual loss. Prompt recognition of the key clinical and laboratory features allows early initiation of corticosteroid therapy with the aim of preventing blindness and other complications. Longer term monitoring and treatment focuses on preventing relapse and minimising harms from prolonged corticosteroid use.

**Aetiology and pathogenesis**

The incidence of GCA increases with age, with mean onset at 72 years. The lifetime risk of developing GCA is estimated as 0.5% for men and 1% for women, making it the most common form of systemic vasculitis. Aetiology is incompletely understood but as with many autoimmune processes, it is likely to involve both a genetic predisposition and an acute trigger. Individuals from Scandinavian descent and those with the HLA-DR4 genotype, which dictates the type and way in which antigens are presented to the immune system, have a higher incidence of the disease. High rates of varicella zoster virus antigen have been found in temporal artery biopsy specimens, suggesting that infection with this virus may be the trigger for onset.

The disease involves local arterial inflammation and systemic upset. Vessel inflammation is mediated by CD4 T-cells, which infiltrate the artery wall, release inflammatory cytokines (including interferon gamma and interleukin 1 ([IL-1])) and recruit macrophages. Multinucleated Langerhans giant cells develop in response to inflammation. Systemic manifestations (including
fever, constitutional symptoms and synovitis) are mediated by cytokines, in particular interleukin 6 (IL-6). IL-6 is also elevated in polymyalgia rheumatica (PMR), and this may explain the high concordance rates between the two diseases.

**Symptoms**

**Classic presentation**
The classic presentation of GCA involves the five cardinal symptoms of headache, jaw claudication, visual changes, pain consistent with PMR and constitutional changes.

**Signs**
- Reduced visual acuity
- Relative afferent pupillary defect
- Visual field defect
- Extraocular motility disturbance

**Fundoscopy and slit-lamp examination**
- Ischaemic optic neuropathy – pale, ‘chalky white’ disc swelling, with or without associated disc/blame haemorrhages and cotton wool spots
- Central retinal artery occlusion – pale retina with a foveal cherry-red spot
- Cilio-retinal artery occlusion (uncommon) – pale retinal ischaemic area from disc to fovea
- Ocular ischaemic syndrome (rare) – anterior uveitis, low intraocular pressure, venous stasis retinopathy

**Investigations**
- Fundus fluorescein angiography – delayed choroidal filling or dark (‘silent’) choroid, disc leak

* Findings listed in order of importance.

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**1. OPHTHALMOLOGICAL FINDINGS IN PATIENTS WITH GIANT CELL ARTERITIS9-11**

**Symptoms**
- Transient vision loss (amaurosis fugax)
- Permanent vision loss
- Diplopia
- Visual field defect

**Signs**
- Reduced visual acuity
- Relative afferent pupillary defect
- Visual field defect
- Extraocular motility disturbance

**Fundoscopy and slit-lamp examination**
- Ischaemic optic neuropathy – pale, ‘chalky white’ disc swelling, with or without associated disc/blame haemorrhages and cotton wool spots
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**POLYMYALGIA RHEUMATICA SYMPTOMS**

About half of patients with GCA report PMR symptoms of pain and morning stiffness of the neck, shoulder and hip girdles. About 14% of patients with isolated PMR will go on to develop GCA.

**Constitutional symptoms**

Fever, weight loss and fatigue occur in up to 60% of patients with GCA. Occasionally GCA may present as pyrexia of unknown origin without other symptoms. Fever is generally low grade, but can exceed 39°C in some cases.

**Rarer presentations**

**Great vessel predominant GCA**

In fewer than 5% of cases, GCA will present with symptoms relating to arteritis of the aorta and thoracic vessels. Patients may complain of arm pain and claudication or experience complications from aortic aneurysms or dissection, including chest pain and heart failure. Internal carotid and vertebral artery involvement can present as acute stroke.

**Other symptoms**

Rarely GCA may present with peripheral synovitis, distal extremity swelling and nonproductive cough (possibly related to cough receptor arterial supply).

**Examination**

Examination of patients with suspected GCA should involve the cranial arteries, pulses and bruits, blood pressure gradient, cardiac auscultation, musculoskeletal system and ophthalmology, as listed in Box 2.

**Investigations**

Further investigations in patients with GCA include blood tests, temporal artery biopsy and imaging.

**Blood tests**

Inflammatory markers (erythrocyte sedimentation rate [ESR] and C-reactive protein [CRP]) are typically elevated in patients with GCA. It is important to note, however, that this is not always the case,
and a normal ESR is seen in up to 4% of patients with biopsy-proven GCA.\(^1\) Raised inflammatory markers are nonspecific and alternative causes, including infection, malignancy and multiple myeloma, also need consideration.

A full blood count (FBC) reveals normocytic anaemia and reactive thrombocytosis in 50% of patients with GCA and leukocytosis in 25% of patients.

Hypoalbuminaemia and an elevated alkaline phosphatase level may be seen in 25% of patients.\(^{14}\)

Blood test results normalise with treatment.

**Cranial arteries**
- Visualise and palpate both temporal arteries for thickening, tenderness, absence of a pulse and adjacent scalp tenderness\(^6\)
- Palpate occipital arteries if occipital headache
(Note that 30% of patients with GCA have a normal temporal artery examination\(^7\))

**Pulses and bruits**
- Palpate the radial, brachial, carotid, femoral, popliteal and pedal pulses for reduced amplitude and delay
- Auscultate the carotid, subclavian, brachial and femoral arteries and the abdominal aorta for bruits

**Blood pressure (BP) gradient**
- Record BP in both arms: a gradient of 10 mmHg or more suggests aortic or subclavian artery disease

**Cardiac auscultation**
- Auscultate for an early diastolic murmur suggestive of aortic regurgitation due to ascending aortic aneurysm

**Musculoskeletal system**
- Assess for reduced active and passive range of motion of shoulders, hips and neck (as with polymyalgia rheumatica)
- Palpate small and large joints for swelling and tenderness

**Ophthalmology**\(^*\)
- Document visual acuity
- Test visual fields and eye movements
- Conduct fundoscopy

* See also Box 1.

**2. ASSESSING PATIENTS WITH GIANT CELL ARTERITIS**

**Figures 2a and b.** a (left) Normal artery. b (right). Artery in giant cell arteritis. (Low power [10x], haemotoxylin and eosin (H&E) stained image.)

**Figures 3a and b.** Artery in giant cell arteritis. a (left). Intimal hyperplasia, fibrin and inflammation through the intima, media and adventitia – medium power (20x). b (right). Acute inflammation including a giant cell within the intima and media – high power (40x). (H&E stained.)

The four key histopathological features of GCA are listed below and shown in Figures 2 and 3:
- Lumen
- Intima
- Elastic lamina (disrupted, fibrin deposition)
- Media (thickened, inflammatory cell infiltrate)

**Temporal artery biopsy**
Ideally all patients with a clinical diagnosis of GCA should undergo temporal artery biopsy for pathological confirmation. This is because the management involves long-term treatment with corticosteroids and many of the symptoms of GCA are nonspecific.

Temporal artery biopsy is usually performed under local anaesthetic by a surgeon or ophthalmologist. A specimen length of greater than 2 cm is required to minimise sampling error. Unilateral biopsy is appropriate for locally symptomatic vessels. Bilateral biopsy may be indicated when there are no lateralisering symptoms or in the case of a negative initial biopsy.\(^{15,16}\) Although the exact rate of complications is not documented, significant bleeding or facial nerve injury are considered rare.\(^{17}\)

The four key histopathological features of GCA are listed below and shown in Figures 2 and 3:
- T cell lymphocyte and macrophage infiltrate
- Intimal and media wall thickening
- Fragmentation of the internal elastic lamina
- Multinucleated giant cells (present in 50% of cases).\(^4\)

The initial biopsy may be negative in up to 15% cases of GCA.\(^{18}\) Negative biopsies may occur due to the patchy nature of vessel involvement or in cases where the aorta and great vessels are the primarily affected sites.\(^{18}\) Thus, when the biopsy is negative
but the clinical picture classic, treatment may still be appropriate.

**Imaging**

Imaging has a limited role in diagnosing typical GCA. Magnetic resonance angiography can show vessel wall oedema and increased gadolinium contrast enhancement in active disease. Magnetic resonance angiography can show vessel wall oedema and increased gadolinium contrast enhancement in active disease. Large vessels in the chest and abdomen may demonstrate increased fluorodeoxyglucose (FDG) uptake on positron emission tomography (PET) scans (Figure 4). Arterial wall thickening, stenosis and a hypoechoic halo (halo sign) have been described on duplex ultrasound examination. As yet, none of these modalities has been shown to be sufficiently reliable as a stand-alone diagnostic test.

**Diagnosis**

Early recognition and diagnosis of GCA is paramount to prevent permanent visual loss, although this can often prove difficult. A definitive diagnosis of GCA can be made in patients with an appropriate clinical picture and positive temporal artery biopsy. The American College of Rheumatology (ACR) classification criteria can assist clinicians in cases of diagnostic uncertainty: three or more of the five criteria should be met for a diagnosis of GCA (Box 3).

**Differential diagnoses**

Important differential diagnoses for GCA depend on clinical presentation. Pathologies that should be considered include:
- transient monocular visual loss – thromboembolic vascular disease, cardiac emboli and primary ophthalmological disease
- elevated ESR – infection, malignancy, multiple myeloma, autoimmune and other vasculitic diseases
- unilateral headache – migraine, tension or cluster headache, herpes zoster, vascular aneurysm/dissection, cervical spine disease and space occupying lesions.

**Management**

The four principles of management in GCA are discussed below and the key steps are outlined in the flowchart.

**Early initiation of corticosteroid and antiplatelet therapy**

Corticosteroids should be commenced immediately in all patients with a high likelihood of having GCA, especially if there is a history of end-organ ischaemia such as visual loss. Aspirin should be added in the absence of contraindications. It is not necessary to wait for the biopsy result as short-term treatment of less than two weeks does not appear to significantly alter histopathological findings.

**Induction (weeks one to four)**

The optimal corticosteroid dosing schedule has not been assessed in clinical trials. The following induction protocol is based on consensus guidelines and may vary slightly between practitioners:

- uncomplicated GCA (no visual loss, although this can often prove difficult. A definitive diagnosis of GCA can be made in patients with an appropriate clinical picture and positive temporal artery biopsy. The American College of Rheumatology (ACR) classification criteria can assist clinicians in cases of diagnostic uncertainty: three or more of the five criteria should be met for a diagnosis of GCA (Box 3).

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**Induction (weeks one to four)**

The optimal corticosteroid dosing schedule has not been assessed in clinical trials. The following induction protocol is based on consensus guidelines and may vary slightly between practitioners:

- uncomplicated GCA (no visual
symptoms, jaw or limb claudication) – prednisone 40 mg/day
• GCA with ischaemic features but without visual loss (e.g. jaw claudication, atypical visual disturbance) – prednisone (or prednisolone) 1 mg/kg up to 60 mg/day
• visual loss (evolving or recent onset) or amaurosis fugax – pulse intravenous methylprednisolone (15 mg/kg to a maximum of 1 g) on days one, two and three, followed by oral prednisone 60 mg/day from day four.23

There should be a marked clinical response to therapy within one week. The diagnosis of GCA should be questioned if there is minimal response. Assuming there is a sufficient response, prednisone is continued at the dose of 60 mg/day for two weeks and then weaned to 40 mg/day by four weeks if disease is stable.

Aspirin 100 mg daily should be added at treatment initiation if there are no contraindications to its use, to potentially reduce the risk of ischaemic vascular events.24,25

**Tapering (weeks five to 52 and beyond):** Prednisone is gradually weaned, with most patients being able to cease therapy within two years.4 There is no defined protocol and treatment should be individualised to the patient. A guide is as follows:22
• weeks five to eight, dose typically weaned from 40 to 20 mg/day
• then decrease by 10 mg every two weeks until 20 mg/day reached
• then decrease by 2.5 mg every two to four weeks until 10 mg/day reached
• then decrease by 1 mg every one to two months, aiming to cease treatment by 12 to 18 months.

**Referral for specialist evaluation and biopsy**
All patients suspected of having GCA should be referred for specialist evaluation and biopsy. This should not delay the initiation of empirical treatment. The role of specialist input is as follows:
• rheumatology – confirmation of diagnosis and exclusion of relevant differentials; assessment and management of disease-related complications; guidance of immunosuppression, adjunctive therapy and treatment of refractory cases
• ophthalmology – urgent assessment of all patients with suspected GCA and visual changes; temporal artery biopsy
4. GIANT CELL ARTERITIS: PRACTICE POINTS

- Giant cell arteritis is a large vessel vasculitis that occurs in people over the age of 50 years.
- High dose corticosteroids should be initiated immediately when the diagnosis is suspected to minimise the risk of visual loss.
- Temporal artery biopsy should be performed to confirm the diagnosis but should not delay the initiation of corticosteroid therapy.
- Referral for specialist evaluation is suggested for all patients.
- Clinicians should implement preventative measures to minimise corticosteroid-related complications.

Monitoring for response to treatment and complications

Monitoring intervals

Patients should be reviewed one week after treatment initiation to confirm response. They are commonly followed up at weeks three, six and 12 and then at three-monthly intervals. Review focuses on the areas below:

- clinical progress – patients should be questioned about new ischaemic symptoms (visual loss, jaw claudication and limb ischaemia) as well as recurrence of original GCA symptoms and side effects of treatment
- blood tests – FBC, electrolytes urea and creatinine, blood glucose level (BGL), CRP and ESR should be checked at each review. Inflammatory markers generally fall quickly with initiation of therapy and normalise after one month; elevations during therapy may indicate relapse or concurrent infection
- aneurysmal disease – a baseline chest x-ray should be performed to check for asymptomatic aortic aneurysmal disease; it is suggested this be repeated every two years up to 10 years.

Complications from long-term corticosteroid use

When initiating long-term corticosteroid treatment in patients, a thorough history and physical examination should be performed to assess for risk factors and pre-existing conditions that may be exacerbated by therapy. Possible complications are listed below:

- Osteoporosis – measurement of vitamin D and calcium levels and bone mineral densitometry (BMD) should be performed at diagnosis. Patients should be treated with oral vitamin D (1000 IU/day) and calcium (600 mg/day) if deficient, and a bisphosphonate added if the patient has had a minimal trauma fracture or their BMD T-score is below 1.5.
- Diabetes – fasting BGL should be measured when therapy is started and patients should be questioned regarding symptoms of hyperglycaemia on subsequent reviews. Levels of blood glucose should be monitored closely in patients who are known to have diabetes and should be checked on follow-up blood testing for other patients.
- Cardiovascular risk – a baseline lipid profile should be obtained after the diagnosis is confirmed and blood pressure should be checked at each clinical review. Statin and/or antihypertensive therapy should be instituted if appropriate.
- Gastric ulceration – a proton pump inhibitor is recommended for gastric protection in patients taking both prednisone and aspirin.
- Exacerbation of psychiatric disease.

Treatment of relapse and refractory disease

Relapse occurs in up to 60% of patients being treated with prednisone for GCA, and is more common at doses below 15 mg/day. Features suggestive of relapse include a recurrence of GCA symptoms and signs and/or an increase in inflammatory markers. Such cases should be discussed with specialists and the patient referred for specialist assessment.

Corticosteroid-sparing immunosuppressive agents may be used in instances of refractory disease or relapse and when clinicians wish to decrease the overall corticosteroid burden. They should only be initiated under the guidance of specialist care. Methotrexate is the best-studied agent and reduces both the relapse rate and cumulative dose of corticosteroids. Small randomised controlled trials have failed to show a convincing benefit from azathioprine and tumour necrosis factor-alpha (TNF-α) inhibitors. Trials are currently in progress to assess the efficacy of IL-6 inhibition with tocilizumab and T cell costimulation blockade with abatacept.

Prognosis

Most patients diagnosed with GCA are able to cease treatment after two years. Some patients require long-term treatment with low dose corticosteroids or corticosteroid-sparing agents. Overall, mortality is higher than in the general population in patients in the first two years after diagnosis of GCA, probably due to coronary vascular disease, but similar thereafter.

Conclusion

GCA is a medium to large vessel vasculitis that characteristically involves the cranial arteries in people over the age of 50 years. Prompt recognition and initiation of corticosteroid-based therapy is required to minimise the risk of irreversible end-organ ischaemia, especially vision loss. Close monitoring with specialist input helps to minimise disease morbidity and treatment related complications. Practice points for GPs are listed in Box 4.

References

A list of references is included in the website version (www.medicinetoday.com.au) and the iPad app version of this article.

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Giant cell (temporal) arteritis
What GPs need to know

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