

An update on the clinical approach to giant cell arteritis

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ABSTRACT

Recent national and international guidance from rheumatology societies have reflected the advances in evidence for both the investigation and management of giant cell arteritis. Cranial ultrasound reduces diagnostic delay and improves clinical outcomes. Immediate high-dose glucocorticoids remain the standard treatment for giant cell arteritis. Randomised controlled trial evidence using tocilizumab, an interleukin-6 receptor antagonist, has been shown to have good clinical efficacy with glucocorticoid sparing effects. Overall patient outcomes appear to be improved by formalising pathways for diagnosis to include clinical experts' opinion early in decision making.

Introduction

Giant cell arteritis (GCA) is caused by systemic granulomatous vasculitis that can affect any size of artery.¹ The incidence of GCA is approximately 1.2 per 10,000 people in the UK and nearly exclusively occurs in people over 50 years old, with the incidence significantly increasing with age. GCA is twice as common in women than men and most commonly affects people of Scandinavian descent.² Seasonality in biopsy-proven GCA is conflicting, some studies indicating a higher occurrence in summer.³ Most physicians will associate new onset headache, scalp tenderness and/or jaw claudication as key clinical features of GCA. However, non-cranial symptoms are common as the clinical spectrum of GCA encompasses three main clinical phenotypes: cranial, large vessel – GCA (LV-GCA) and polymyalgia rheumatica (PMR), with a complex overlap existing in some patients. Diagnosis of GCA is challenging because of the extensive disease heterogeneity. In addition, there is no specific accessible biomarker that can definitively diagnose GCA.¹

GCA is a medical emergency as it can lead to sudden, permanent blindness.^{4–6} European guidance has recommended the first-line investigations of ultrasound of the temporal arteries.⁴ The mainstay of treatment is the immediate initiation of high-dose glucocorticoids (GC). However, GC toxicity is now well recognised and alternative therapies have, therefore, been introduced

alongside a concomitant GC-tapering regimen. Recently published guidelines and recommendations on the diagnosis and management of GCA are changing clinical practice and are summarised herein.^{4–6}

Diagnosis

History

Cranial symptoms include new onset headache, temporal cutaneous hyperalgesia and jaw/tongue claudication. Ophthalmic features include transient monocular loss of vision (amaurosis fugax) and transient or persistent diplopia, usually preceding permanent loss of vision. Rarely, bilateral visual disturbances or flashes can be a sign of vertebral artery vasculitis.⁷ Associated features of large- and medium-vessel involvement include systemic symptoms such as fever, myalgia, fatigue, night sweats, loss of appetite, unintentional

Key points

Tests, including non-invasive imaging, in conjunction with clinical expertise are the current gold standard for diagnosis of giant cell arteritis.

Fast-track pathways reduce giant cell arteritis-related morbidity (such as visual loss), reduce the potential for over treatment in those with suspected giant cell arteritis and are cost effective.

Ultrasound can be time consuming but is non-invasive, repeatable and can examine multiple arterial territories.

Positron emission tomography – computed tomography is beneficial in terms of visualising the inflammation in the arterial tree, but also may be helpful early in the diagnostic pathway to uncover alternative diagnoses.

Use of tocilizumab, an interleukin-6 inhibitor, is based on randomised controlled trial evidence of its efficacy in achieving remission with significant glucocorticoid sparing over the course of 12 months.

KEYWORDS: giant cell arteritis, temporal arteritis, tocilizumab, temporal artery biopsy, ultrasound

DOI: 10.7861/clinmed.2022-0041

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weight loss and mood change.⁶ There is an established association of GCA with PMR and so there should be a low threshold of suspicion in these patients presenting with symptoms of GCA.⁸ Presence of ophthalmic symptoms should prompt immediate specialist referral to prevent permanent sight loss.

Examination

Examination of GCA is symptom-dependent and may include targeted examination such as an ophthalmic examination or comprehensive arterial examination.

Case study: A 72-year-old woman was referred acutely to the ophthalmology department under suspicion of left retinal detachment. Prior to the referral, C-reactive protein (CRP) had been elevated for some time; last measured at 126 mg/L (normal range <10). She had no fever and no sign of infectious focus. She experienced a sudden painless loss of vision in the left eye, and a few days later sudden vision loss in the right eye. When asked, the patient had experienced jaw claudication for days and shoulder–neck pain and fatigue for months. On examination, CRP was elevated at 93 mg/L and erythrocyte sedimentation rate (ESR) was 94 mm/hour (normal range ≤ 20.5). Both temporal arteries were thickened with low pulsation. Ophthalmic examination showed that best-corrected visual acuity was 0.3 right eye and hand motion left eye. Pupils were isocoric with a left relative afferent pupillary defect. Treatment with high-dose glucocorticoids was initiated immediately on suspicion of cranial GCA (Fig 1).

Where vision is affected, an assessment of the visual acuity may find profound visual loss secondary to an ischaemic optic neuropathy. Double vision may be the result of a third, fourth or sixth cranial nerve palsy. Where left ventricle disease is suspected, a comprehensive pulse assessment, bruit auscultation and inter-arm systolic blood pressure difference should all be assessed. In any scenario where GCA is suspected, palpation of the temporal arteries may find prominence, beading and reduced or absent pulse.⁶

Investigations

Prompt diagnosis of GCA is crucial to prevent sight loss, however, one study reported a mean diagnostic delay from symptom onset to diagnosis to be 9 weeks and significantly longer if cranial symptoms were absent, there was no diagnosis of PMR or the patient age was <70 years old.⁹ Rapid access clinics with onsite ultrasound have been shown to reduce diagnostic delay and, therefore, reduce GCA-related visual loss.^{6,10} Patients presenting with new-onset visual loss or diplopia should be referred on the same day for an ophthalmology assessment. Crucially, where there is a strong clinical suspicion of GCA, GC should be given without waiting for the tests to return.

Bloods

Most patients with GCA have raised inflammatory markers (such as CRP and ESR) or plasma viscosity. However, cases with normal ESR can occur.¹¹ These markers are limited in that they are not sensitive to GCA or indicative of prognosis.⁶ In fact, up to 10% of cases present with normal ESR and, in this study, higher inflammatory markers correlated with fewer ischaemic events.⁶ Raised ESR can also be found for mimics of GCA such as neurological infections and paraneoplastic disorders causing headache and visual disturbances. Therefore, it is recommended that these tests alone are not used to make a diagnosis of GCA but may support a clinical diagnosis.

Ultrasound

Colour Doppler ultrasound (CDUS) has been recommended as an initial, non-invasive investigation.⁶ CDUS assesses arterial wall anatomy, lumen patency and blood flow. Positive findings include the halo sign and the compression sign. The halo sign (homogeneous, hypoechoic circumferential vessel wall thickening) has a sensitivity of 68% and a specificity of 91%, which was increased to 100% when found bilaterally (Fig 2).¹² The Halo Score has recently been developed to quantify vascular

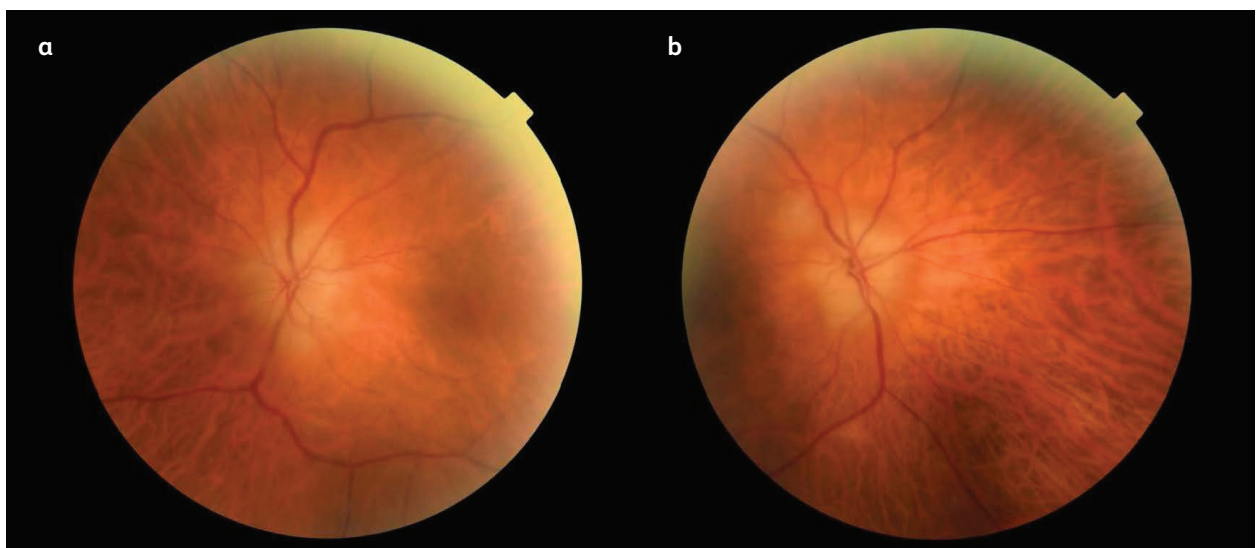


Fig 1. Fundus photography of optic discs showing pale optic disc oedema. a) Left eye. b) Right eye.

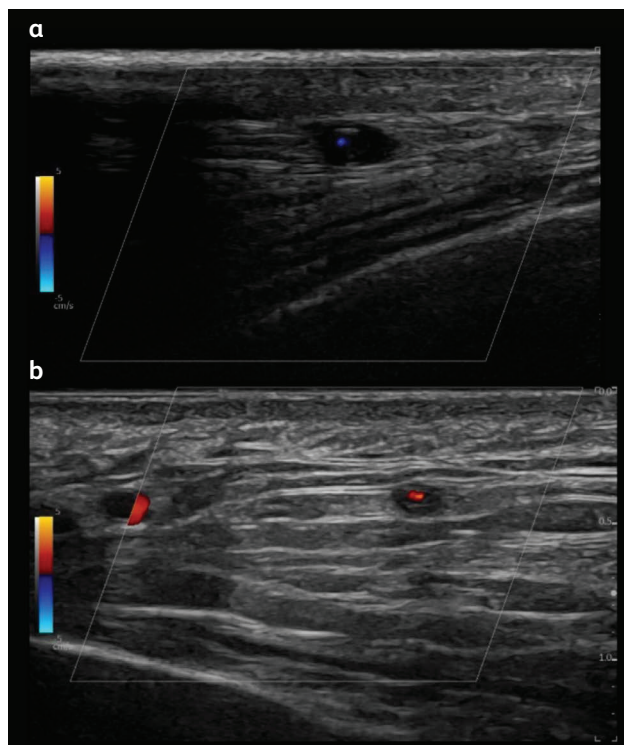


Fig 2. Colour Doppler ultrasound of the temporal arteries showing halo sign. a) Left temporal artery. b) Right temporal artery. Image courtesy of Dr Viktoria Fana.

inflammation and is useful to establish a diagnosis of GCA as well as characterise the risk of ocular ischaemia.¹³ The compression sign describes the ability of a normal artery to extinguish with pressure as opposed to a vasculitic artery that will not, and is useful to distinguish a true versus a false halo.¹⁴ In a recent comparative study, the sensitivity of CDUS was found to be almost on par with that of temporal artery biopsy (TAB), although the overall diagnostic accuracy of CDUS was slightly lower. For a number of centres, CDUS has reduced the requirement for TAB.¹⁵

Temporal artery biopsy

TAB has a high specificity, however, studies have reported a great variation in this, between 39%–90% (Fig 3).¹⁴ There is high heterogeneity because a positive TAB is influenced by biopsy length, the variation in histological interpretation, biopsy cuts and glucocorticoids. Histological findings include extensive inflammatory infiltrates, granulomas and nucleated giant cells.¹⁶ However, TAB is a surgical procedure (invasive) and lacks sensitivity, particularly when dealing with extra-cranial disease.¹⁴

Positron emission tomography – computed tomography

Positron emission tomography – computed tomography (PET-CT) on a time-of-flight scanner with fluorine-fluorodeoxyglucose (F-FDG) administration and 1 mm CT slice thickness allows assessment of disease activity from FDG vessel uptake (Fig 4). F-FDG-PET is recommended for patients presenting with suspected involvement of thoracic and vertebral vessels where CDUS cannot adequately

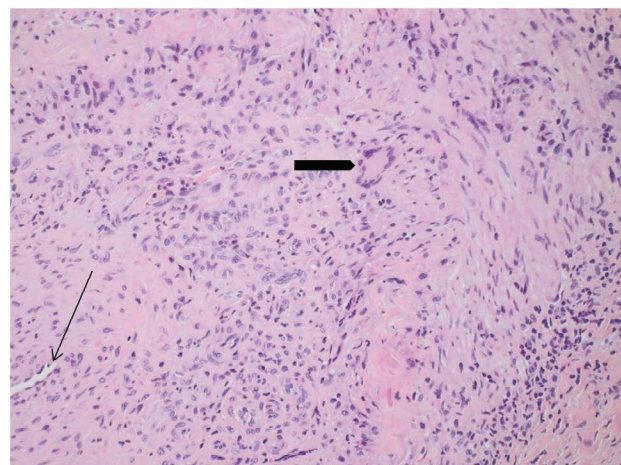


Fig 3. Temporal artery biopsy showing thickened intima and a narrowed lumen (thin arrow); the elastic lamina is fragmented with transmural inflammation and giant cells (thick arrow).

image these deeper vessels.⁵ The Giant Cell Arteritis and PET Scan (GAPS) study found a sensitivity of 92% and specificity of 85%. In addition, the use of PET allowed for other mimics of GCA to be diagnosed early.¹⁷

Management

Immediate

Immediate glucocorticoid prescription is recommended where GCA is confirmed or strongly suspected.¹⁰ The dosing is initially with oral prednisolone 40–60 mg daily.^{5,6,10} If symptoms of cranial ischaemia, including visual disturbance, are present, it is recommended to use a 500–1,000 mg intravenous prednisolone induction dose for 3 days followed by a reduction course.^{5,6,10}

Long term

The adverse effects of high-dose and long-term GC use are well established and include cushingoid-like syndrome, hyperglycaemia, osteoporosis and dyspepsia among others.^{5,10} Hyperglycaemia and hypertension should be assessed within 2 weeks of starting prednisolone.^{5,10} To prevent long-term steroid-related complications, a GC-tapering regimen over 6–24 months according to response (symptoms and inflammatory markers) is recommended.^{4,6}

Relapse of GCA is common and flares are treated by increasing GC dose, elongating treatment.^{4,6} Prescription of methotrexate is recommended alongside a GC-tapering regimen in those with a high risk of GC toxicity or relapse to reduce the cumulative GC dose and prevent relapse.^{5,6,10} There is insufficient evidence to recommend the use of other oral immunosuppressive agents (such as azathioprine, leflunomide or mycophenolate mofetil) in GCA.^{4,6}

There is class 1 evidence to support the use of tocilizumab, an interleukin-6 inhibitor, in combination with GC-tapering to reduce GC-toxicity and prevent relapse.¹⁸ Adverse effects include headache, exacerbation of diverticular disease, transient neutropenia, elevated triglycerides and deranged liver function tests, which more commonly affect elderly patients as in GCA.¹⁹ Other biologics, such as tumour necrosis factor inhibitors, are not recommended in GCA.⁵

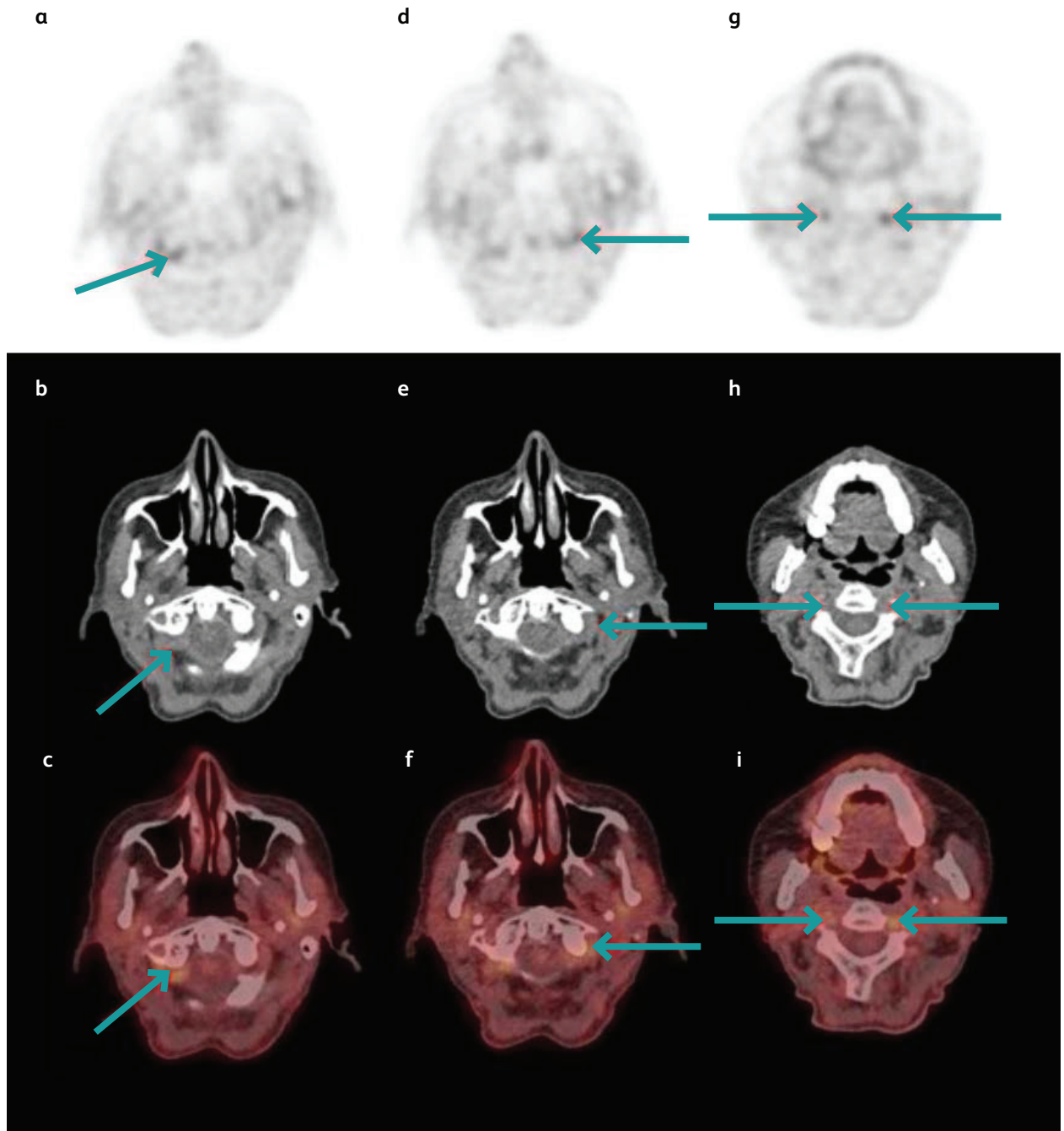


Fig 4. Panels a, b and c show increased $2\text{-}^{18}\text{F}$ -fluorine-fluorodeoxyglucose (F-FDG) uptake in the right vertebral artery where it enters the foramen magnum through the right suboccipital triangle (arrow). Panels d, e and f show increased $2\text{-}^{18}\text{F}$ -FDG uptake in the left vertebral artery where it enters the foramen magnum through the left suboccipital triangle (arrow). Panels g, h and i show increased $2\text{-}^{18}\text{F}$ -FDG uptake in the right and left vertebral artery in the transverse foramina of the C2 (arrows). a, d and g) Axial $2\text{-}^{18}\text{F}$ -FDG positron emission tomography. b, e and h) Axial low-dose computed tomography (IdCT). c, f and i) Axial fused $2\text{-}^{18}\text{F}$ -FDG PET-IdCT. Images and description courtesy of by Dr Jane Maestri Brittain.

Adjuvant therapies

Adjuvant therapies to target the side-effect profile of GC therapy have been considered. Similar to other conditions that require long-term GC use, proton pump inhibitors and bisphosphonates are recommended.⁵ There is insufficient evidence to support the routine use of cholesterol-

lowering agents, such as statins, in GCA.⁵ A systematic review that searched for randomised controlled trials on the effectiveness of aspirin use in GCA yielded no results.²⁰ Therefore, there is insufficient evidence to recommend the commencement of anti-platelet or anticoagulant therapy for a new diagnosis of GCA.^{4,5}

GCA and COVID-19

The COVID-19 pandemic has had a significant impact on the delivery of healthcare, and may have led to diagnostic delay for those with GCA. Initial consultations became via telephone, which introduced clinical uncertainty as overlap between GCA and COVID-19 exists. While acute-onset headache, fever, fatigue, myalgia and elevated inflammatory markers are typical commonalities, dry cough and isolated dyspnoea are rare in GCA.²¹ ■

Acknowledgements

Thanks to Dr. Viktoria Fana for the ultrasound image (Fig 2) and to Dr Jane Maestri Brittain for the PET-CT image and description (Fig 4).

Conflicts of interest

Susan P Mollan reports advisory board and speaker fees from Roche (2016–2019); speaker fees from Chugai–Roche (2017–2019); and advisory board fees from Janssen (2020); and was an investigator in a clinical trial in GCA with Roche.

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