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Giant cell arteritis is the principal form of systemic vasculitis affecting people over 50. Large-vessel involvement, termed large vessel giant cell arteritis, mainly affects the aorta and its branches, often occurring alongside cranial giant cell arteritis, but large vessel giant cell arteritis without cranial giant cell arteritis can also occur. Patients mostly present with constitutional symptoms, with localising large vessel giant cell arteritis symptoms present in a minority of patients only. Large vessel giant cell arteritis is usually overlooked until clinicians seek to exclude it with imaging by ultrasonography, magnetic resonance angiography (MRA), computed tomography angiography (CTA), or [^{18}F] fluorodeoxyglucose-PET-CT. Although the role of imaging in treatment monitoring remains uncertain, imaging by MRA or CTA is crucial for identifying aortic aneurysm formation during patient follow up. In this Series paper, we define the large vessel subset of giant cell arteritis and summarise its clinical challenges. Furthermore, we identify areas for future research regarding the management of large vessel giant cell arteritis.

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This is the fourth in a **Series** of six papers on vasculitis. All papers in the Series are available at thelancet.com/series/vasculitis

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Introduction

Giant cell arteritis is an immune-mediated vasculitis predominantly affecting medium-sized cranial arteries (cranial giant cell arteritis) and medium-sized to large-sized arteries in the torso, limbs, and neck (figure 1). The giant cell arteritis subset affecting the torso, limbs, and neck is often referred to as extracranial or large vessel giant cell arteritis (the term used in this Series paper). It should be noted that the 2012 Chapel Hill criteria do not provide a precise definition of large vessel giant cell arteritis,[1] and that large vessel giant cell arteritis can involve medium-sized arteries that are partly located intracranially. Mixed cranial and large vessel giant cell arteritis is seen in more than half of patients, whereas giant cell arteritis limited to either cranial arteries (limited cranial giant cell arteritis) or arteries in torso, limbs and neck (limited large vessel giant cell arteritis) occur less frequently. Giant cell arteritis develops after the age of 50 years and is more common in women than men. Giant cell arteritis is often associated with polymyalgia rheumatica, typically causing inflammation of musculoskeletal structures in the shoulder and hip girdle. Given their extensive overlap, it has been suggested to combine the two conditions under the common term giant cell arteritis and polymyalgia rheumatica spectrum disease.[2]

Interest in large vessel giant cell arteritis was historically overshadowed by a greater focus on cranial giant cell arteritis, with modern imaging techniques permitting a richer understanding of large vessel giant cell arteritis only after their gradual adaptation during the last two decades.[3] The first description of giant cell arteritis, in 1890, was a patient with temporal arteritis. Publications on large vessel giant cell arteritis emerged in the 1930s with autopsies showing aortic, carotid artery, and iliac artery involvement. Large vessel giant cell arteritis has been overlooked for decades because of the absence of localised symptoms, with temporal artery biopsy being the main diagnostic test during the last century. The emphasis on cranial giant cell arteritis is also reflected by the classification criteria, which primarily contain items related to cranial giant cell arteritis.[4,5] Only in the last decade has interest in large vessel giant cell arteritis increased. Before 2018, only 24 studies in PubMed mentioned large vessel giant cell arteritis in their title or abstract. As of Sept 27, 2023, an additional 59 studies have been published. It is important to note that in many studies on large vessel giant cell arteritis, comprehensive assessments for both large vessel giant cell arteritis and cranial giant cell arteritis were not performed. Thus, studies of large vessel giant cell arteritis might have included patients with cranial involvement, and vice versa.

Although current evidence suggests that large vessel giant cell arteritis and cranial giant cell arteritis are partly overlapping disease subsets, each has its own clinical challenges. In this Series paper, we provide an overview on the epidemiology, pathobiology, diagnostic aspects, and management of large vessel giant cell arteritis. The cranial subset of giant cell arteritis is discussed in the third paper in this Series.

Epidemiology

Research suggests that patients with large vessel giant cell arteritis are younger than patients with cranial giant cell arteritis.[6] A meta-analysis showed an age difference of 4·5 years between the two subsets.[7] A 2023 study found that patients younger than 64 years more often had large vessel giant cell arteritis, and patients older than 79 years were more likely to have cranial giant cell arteritis.[8] Large vessel giant cell arteritis appears to disproportionately affect women compared with cranial giant cell arteritis.[7]

Current evidence suggests that the incidence of large vessel giant cell arteritis is lower than that of cranial giant cell arteritis, although undiagnosed large vessel giant cell arteritis could exist in the community.[9] In France, the annual incidence of limited large vessel giant cell arteritis

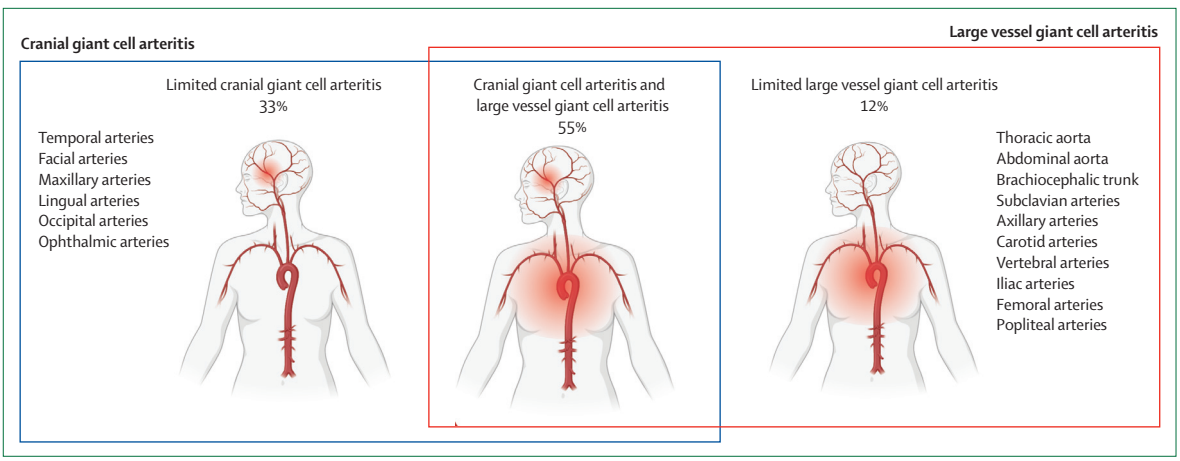

Figure 1: **Distribution of large vessel and cranial artery involvement in giant cell arteritis**
The large vessel giant cell arteritis subset includes the medium-sized and large-sized arteries in the torso, neck, and limbs. Large arteries have a high elastic tissue content. Medium-sized arteries have a more well developed muscular layer and are located further from the heart. The most distal parts of two medium-sized arteries (vertebral and internal carotid arteries) are located intracranially. Estimates of the prevalence of limited cranial giant cell arteritis, limited large vessel giant cell arteritis, and mixed cranial giant cell arteritis and large vessel giant cell arteritis were calculated by pooling 241 patients from four prospective studies that were retrieved via our search strategy.[6,13-15] Created with BioRender.com.

was estimated at 0·6 per 100 000 people over the age of 50 years, whereas the incidence of cranial giant cell arteritis (limited cranial giant cell arteritis or mixed cranial giant cell arteritis and large vessel giant cell arteritis) was 7·6 per 100 000 people over the age of 50 years.[10] An Italian study reported an annual incidence of 3·4 per 100 000 people aged 50 years or older for large vessel giant cell arteritis (limited large vessel giant cell arteritis or mixed large vessel giant cell arteritis and cranial giant cell arteritis), compared with 6·1 per 100 000 people aged 50 years or older for limited cranial giant cell arteritis.[11] However, neither of these studies examined the possibility of both cranial and large vessel involvement in every individual. A third study, performed in Slovenia, reported the incidence of giant cell arteritis in patients who were all thoroughly screened for cranial giant cell arteritis and large vessel giant cell arteritis.[12] The annual incidence was 2·2 per 100 000 people aged 50 years or older for large vessel giant cell arteritis (limited large vessel giant cell arteritis or mixed large vessel giant cell arteritis and cranial giant cell arteritis) and 6·5 per 100 000 people aged 50 years or older 50 years for limited cranial giant cell arteritis. Overall, these epidemiological studies indicate that cranial giant cell arteritis is more common than large vessel giant cell arteritis.

Prospective cohort studies provide further insight into the relative distribution of large vessel giant cell arteritis and cranial giant cell arteritis. Prieto-González and colleagues observed large vessel giant cell arteritis on CT in 27 (68%) of 40 consecutive patients with temporal artery biopsy-positive giant cell arteritis.[13] Similarly, Agard and colleagues found aortic involvement on CT in ten (45%) of 22 patients with temporal artery biopsy-proven giant cell arteritis.[14] Nielsen and colleagues reported that 42 (91%) of 46 patients with [^{18}F]fluorodeoxyglucose ([^{18}F]FDG)-PET-CT-confirmed large vessel giant cell arteritis also had cranial giant cell arteritis at diagnosis.[15] Nielsen and colleagues' diagnosis of cranial giant cell arteritis was based on the 1990 American College of Rheumatology (ACR) criteria for giant cell arteritis, with confirmation by temporal artery imaging or biopsy in most patients. Bull Haaversen and colleagues performed extensive ultrasonographic assessment of temporal arteries and large vessels in 133 consecutive patients with new-onset giant cell arteritis,[6] and observed limited large vessel giant cell arteritis in 21 (16%) patients, mixed large vessel giant cell arteritis and cranial giant cell arteritis in 72 (54%) patients, and limited cranial giant cell arteritis in 40 (30%) patients. By combining the data from these studies, the results suggest that most patients have mixed large vessel giant cell arteritis and cranial giant cell arteritis (figure 1).

Pathobiology

Genetics

Existing literature on the genetics of large vessel giant cell arteritis and cranial giant cell arteritis is scarce. One study suggested that different *HLA-DRB1*04* variants were associated with large vessel giant cell arteritis and cranial giant cell arteritis.[16] However, another study showed that *HLA-DRB1*0401* and *HLA-B*15:01* were equally over-represented in patients with cranial giant cell arteritis or large vessel giant cell arteritis compared with healthy controls.[17] The frequency of specific interleukin (IL)-6 and IFN-γ polymorphisms was also shown to be similar in both giant cell arteritis subsets.[18,19] Thus, no genetic differences between large vessel giant cell arteritis and cranial giant cell arteritis have been observed in the scarce literature available.

Histology of large vessel giant cell arteritis

Histological studies on large vessel giant cell arteritis mostly rely on aortic specimens from patients requiring surgery for aortic complications. Lymphoplasmacytic infiltrates with minimal fibrosis characterise the adventitial pathology of the aortitis. These infiltrates, predominantly composed of T cells, B cells, and, to a lesser extent, plasma cells, present various degrees of organisation, ranging from an unorganised diffuse pattern to well organised tertiary lymphoid organs with germinal centres.[20] The media shows granulomatous inflammation with macrophages, T cells, and occasional giant cells (figure 2).[21] The infiltrate is usually accompanied by laminar medial necrosis, a non-specific pathological feature, with largely acellular areas in the media reflecting a loss of smooth muscle cells and the collapse of elastic fibres. In more advanced stages of large vessel giant cell arteritis, an aortic aneurysm can develop as a complication of inflammation and abnormal remodelling. Finally, the innermost layer of the arterial wall often shows intimal hyperplasia. Autopsy reports by Östberg and colleagues revealed similar histological findings in other large vessels affected by large vessel giant cell arteritis.[22]

The histology of aortitis due to giant cell arteritis can appear differently from that in cranial giant cell arteritis, with the latter primarily being studied in the temporal arteries. Prominent destruction of the media seen in the aorta is not a common finding in temporal arteries. However, early reports from an era when awareness of giant cell arteritis was low and glucocorticoid treatment was unavailable, underscored that prominent media destruction could eventually occur in the temporal arteries.[23] Current discrepancies in the histology of aortitis and temporal arteritis could reflect the different disease stages in which the respective tissues are obtained.

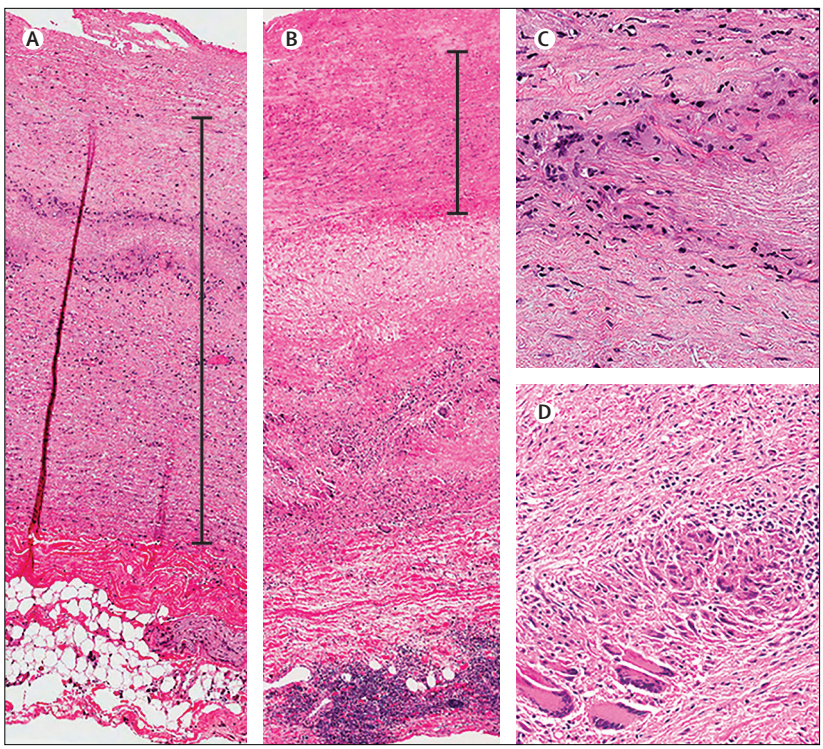

Figure 2: **Pathology of large vessel giant cell arteritis and Takayasu arteritis**
In large vessel giant cell arteritis (A) the inflammation tends to involve the inner half of the media most severely, in contrast to Takayasu arteritis (B), in which the inflammation most severely involves the outer half of the media and adventitia. The brackets demarcate the media. At higher magnification, giant cells can be seen in both large vessel giant cell arteritis (C) and Takayasu arteritis (D), but compact granulomas are more commonly seen in Takayasu arteritis. Adapted from Stone and colleagues with permission from the publisher.[21]

Comparison with histology of other diseases affecting the aorta

The histological changes in aortitis due to giant cell arteritis might differ from those in other inflammatory diseases.[21] Although giant cell arteritis tends to involve the inner half of the media in the aorta, the outer half is typically most involved in Takayasu arteritis.[21] Compact granulomas and adventitial scarring are more typical of Takayasu arteritis than of giant cell arteritis (figure 2). Large vessel vasculitis due to granulomatosis with polyangiitis (GPA) can also show granulomatous inflammation. Unlike giant cell arteritis, the giant cells in GPA are not specifically associated with elastic fibres. There are usually more neutrophils and necrosis in GPA than in giant cell arteritis. Neutrophils might also be present in cases of aortic dissection. Compact granulomas typical of sarcoidosis are usually absent in giant cell arteritis. Aortitis due to IgG4-related disease shows lymphoplasmacytic inflammatory infiltrates, obliterative adventitial phlebitis, and fibrosis, which can adopt a storiform pattern.[24] Granulomatous inflammation is not a feature of IgG4-related disease. Most patients with clinically isolated aortitis in the USA and Europe have pathological features indistinguishable from those of large vessel giant cell arteritis.[25] The transcriptome of clinically isolated aortitis is identical to that of aortitis due to giant cell arteritis, further suggesting that clinically isolated aortitis is a subset of giant cell arteritis.[26] Some older patients with clinically isolated aortitis develop systemic disease leading to a diagnosis of giant cell arteritis.[27] Features of atherosclerosis are common in aortic tissue affected by giant cell arteritis. Differentiation of giant cell arteritis from atherosclerosis-associated inflammation might be difficult in the absence of giant cells, particularly if the atherosclerosis is severe.[21] Tertiary lymphoid organs could be present in the adventitial layer of patients with atherosclerosis, as well as those with large vessel giant cell arteritis.[20]

Immunology

Temporal artery biopsy studies have revealed a prominent role for vascular dendritic cells, T helper 1 cells, T helper 17 cells, and macrophages in the pathogenesis of giant

cell arteritis.[2] Vascular dendritic cells, which could initiate the inflammatory cascade in temporal arteries, are also present in the adventitia of the extracranial arteries. Expression of Toll-like receptors by vascular dendritic cells differs among arterial territories.[28] Thus, unique molecular triggers could potentially activate vascular dendritic cells in specific arterial beds. A type 1 interferon signature has been found in aortic tissue affected by large vessel giant cell arteritis.[29,30] T helper 1 cells and cytotoxic T cells can cause a prominent IFN-γ response in aortitis due to giant cell arteritis.[31,32] These cells are attracted by CXCL9 and CXCL10, which are highly expressed in the inflamed aortic wall.[26,33] Uncontrolled T-cell activation has been linked to a paucity of regulatory T cells and deficient expression of PD-1 in the aortic tissue.[32] Granulocyte-macrophage colony-stimulating factor is highly expressed in aortitis due to giant cell arteritis and skews macrophages towards the production of YKL-40, which induces a subsequent subset of macrophages to secrete tissue-destructive MMP-9.[34,35] Prominent B-cell infiltrates are present due to high expression of CXCL9 and CXCL13.[26,33,36] These cells can organise into tertiary lymphoid structures, which most likely contribute to the sustained inflammatory response.[20,36,26]

	Total number of patients with large vessel giant cell arteritis in studies	Presence among patients with large vessel giant cell arteritis, median % (range)*
Constitutional symptoms[6,16,37–39]	466	66 (31–68)
Polymyalgia rheumatica[6,16,38,39,49]	374	38 (21–45)
Arm claudication[37,41]	199	16 (5–28)
Leg claudication[37]	145	4
Raynaud's-like phenomenon[39,42,43]	179	19 (11–22)†
Bruits[37]	145	17
Abnormal pulse in arms[37]	145	8
Abnormal pulse in legs[37]	145	13
Absent blood pressure in arms[37]	145	1
Blood pressure difference in arms[37]	145	18

Blood pressure difference between both arms was defined as 10 mm Hg or more; pulse abnormality was defined as diminished or absent pulse in the upper limbs (subclavian, axillary, brachial, or radial arteries) or lower limbs (femoral, popliteal, posterior tibial, or dorsalis pedis arteries); bruits were recorded in the abdominal aorta or carotid, subclavian, axillary, or renal arteries. Studies in which patients were selected for the presence of symptoms or arterial involvement were excluded, unless no studies would remain available (eg, studies on Raynaud's-like phenomenon). When multiple studies reported overlapping patient samples, data from the largest or most recent study were selected. *Range unavailable in some cases due to data being extracted from a single study. †In selected patients with arm involvement.

Table: **Symptoms and physical signs in patients with large vessel giant cell arteritis**

Clinical aspects

Symptoms

Patients with large vessel giant cell arteritis have longer diagnostic delays than patients with cranial giant cell arteritis.[7] Constitutional symptoms are a common presenting feature in large vessel giant cell arteritis (table).[6,16,37–39] Weight loss is more frequently seen than night sweats and fever.[37] The presence of constitutional symptoms does not distinguish patients with large vessel giant cell arteritis from those with cranial giant cell arteritis;[6,7] however, a dry cough might be more prevalent among patients with large vessel involvement.[15,40] Identification of symptoms that place large vessel giant cell arteritis high on the differential diagnosis are typically absent, and therefore a strong clinical intuition is often essential in even considering the diagnosis. Stenosis or occlusion of vessels supplying the limbs can cause limb claudication[37,41] and symptoms in the digits that mimic Raynaud's phenomenon.[39,42,43] If present, limb claudication has a high predictive value for a diagnosis of giant cell arteritis.[44] One study showed improvement of these symptoms in five (31%) of 16 patients during treatment.[38] Ischaemic ulcerations and necrosis of the extremities are rare because of the exuberant collateral circulation that develops in large vessel giant cell arteritis.[38] Aortic involvement might be associated with chest, abdominal, or back pain in 32% of patients.[45] Carotidynia is rarely seen, but posterior neck pain can develop in conjunction with vertebral artery involvement.[41] In a meta-analysis, neck pain was identified as one of a few symptoms that could increase the likelihood of giant cell arteritis in a diagnostic setting.[44]

Although vertebral artery involvement is considered part of large vessel giant cell arteritis (figure 1), it is associated with the ischaemic manifestations of cranial giant cell arteritis. Even though the presence of other large vessel involvement (such as the aorta) is associated with a low risk of cranial ischaemic manifestations, vertebral arteritis has been linked to a high risk of such complications.[46] Vertebral artery involvement is the main cause of ischaemic stroke in patients with large vessel giant cell arteritis, a rare but feared complication.[47] Hence, stroke in giant cell arteritis primarily affects the posterior cerebral circulation. The wider risk of cranial ischaemic symptoms is also increased in patients with giant cell arteritis-related stroke. A report of 40 patients with giant cell arteritis-related stroke, mostly caused by vertebral artery involvement, found ophthalmic ischaemic symptoms in 25 (63%) of these patients, versus 50 (25%) in 200 patients with giant cell arteritis without stroke.[47]

Physical examination

Careful physical examination can provide important clues to the presence of large vessel giant cell arteritis. Physical examination might reveal reduced or absent pulsations at the extremities, blood pressure differences

between the arms, and bruits over the large vessels (table).[37] Occasionally, blood pressure cannot be measured in the arms due to severity of the stenosis. Using angiography as the reference standard, the sensitivity of these findings is low, but the specificity is high.[48] Aortic valve regurgitation can develop in patients with an aneurysm of the ascending aorta.

Laboratory testing

Inflammatory markers such as C-reactive protein and erythrocyte sedimentation rate are usually elevated in large vessel giant cell arteritis, but do not discriminate well from cranial giant cell arteritis.[6,37] Inflammation can also lead to anaemia and thrombocytosis.[44] Alternative diagnoses should be excluded depending on the clinical presentation. Serology for other vasculitides (eg, antineutrophil cytoplasmic antibodies or IgG4) and infections (eg, syphilis, Q fever, or mycobacterium) should be considered. In patients with new-onset Raynaud's phenomenon, it might be warranted to perform serological testing (antinuclear antibodies and antibodies to extractable nuclear antigens) for other associated systemic autoimmune diseases. In patients with digital ischaemia, extensive coagulation testing might be required to rule out other conditions causing such vascular events. Assessment for VEXAS syndrome, which primarily affects men, might be appropriate when other autoinflammatory or myelodysplastic features are present, or in cases of refractory giant cell arteritis.

Relationship with polymyalgia rheumatica

Polymyalgia rheumatica is present in 38% of patients with large vessel giant cell arteritis (table)[6,16,38,39,49]; similar rates are also seen in patients with cranial giant cell arteritis.[6] Large vessel giant cell arteritis often goes undetected as large vessel imaging studies are not routinely done in patients presenting with polymyalgia rheumatica. A 2023 study showed that 23% of patients with polymyalgia rheumatica have so-called clinically occult giant cell arteritis as indicated by extensive vascular ultrasonography,[50] although concealed giant cell arteritis might be a more accurate term. Many of these patients had large vessel giant cell arteritis: 39% limited large vessel giant cell arteritis, 33% mixed large vessel giant cell arteritis and cranial giant cell arteritis, and 28% limited cranial giant cell arteritis.[50] The presence of constitutional symptoms is not predictive of concealed giant cell arteritis in patients with polymyalgia rheumatica.[6,51] One study suggested that bilateral and diffuse pain in the lower limbs of patients with polymyalgia rheumatica is associated with large vessel giant cell arteritis.[51] Novel biomarkers in blood (eg, angiopoietin-2 to angiopoietin-1 ratios and MMP-3 concentrations) might serve as an early warning sign of concealed giant cell arteritis in patients with polymyalgia rheumatica,[52,53] but these reports require additional confirmation. The identification of large vessel giant cell arteritis could potentially influence the decision to start glucocorticoid-sparing therapy in individuals with polymyalgia rheumatica given their longer glucocorticoid requirements,[52] and could prompt evaluation of aortic damage.

Imaging

Given the protean, non-specific manifestations of giant cell arteritis, the diagnosis should be confirmed by imaging or biopsy where possible. The European League Against Rheumatism (EULAR) recommends ultrasonography of the temporal and axillary arteries as the first test for suspected giant cell arteritis.[54] In contrast, the ACR still advocates for temporal artery biopsy as the initial test.[55] This difference reflects the better access to well-trained vascular ultrasonographers in Europe. [^{18}F]FDG-PET-CT magnetic resonance angiography (MRA), and computed tomography angiography (CTA) are also used for the evaluation of possible large vessel giant cell arteritis. High-resolution MRI and newer generations of [^{18}F]FDG-PET-CT scanners can aid the diagnosis of cranial giant cell arteritis. The diagnostic strategy for individual patients depends on whether the major clinical symptoms are more suggestive of either cranial giant cell arteritis or large vessel giant cell arteritis, prompt availability of the tests, and other factors (panel). Imaging should ideally be done within 72 h of high-dose glucocorticoid therapy initiation because treatment alters the imaging characteristics of affected blood vessels.[54] Irrespective of the imaging method used, large vessel giant cell arteritis is typically characterised by homogenous, concentric lesions in long arterial segments. Inhomogeneous, eccentric, and patchy lesions are usually suggestive of atherosclerosis. Standardisation is warranted in the use of repetitive imaging, considering variations in scanners, software, and operators. There is a need for imaging tests with a longer diagnostic window after therapy initiation, as immediate access to the various imaging tools (within 72 h of treatment) is not always available. One promising test is PET-CT using alternative radiotracers (not [^{18}F]FDG) that directly detect specific immune cells,[56] which are known to persist in the arterial wall for an extended period after intiation of therapy.[57]

Heterogeneity exists regarding the vessels involved in patients with large vessel giant cell arteritis. The most commonly affected arteries are the thoracic aorta (73%), subclavian arteries (58%), brachiocephalic trunk (innominate artery; 58%), and axillary arteries (48%).[7] Ultrasound studies suggest more frequent involvement of the axillary than subclavian arteries,[6,58,59] probably reflecting the greater ease and resolution by which this artery can be examined. Ultrasonography has a 62–76% sensitivity for detecting axillary artery inflammation when using [^{18}F]FDG-PET-CT of axillary arteries as a reference standard.[15,60] Thus, [^{18}F]FDG-PET-CT might still be appropriate when an ultrasound scan of the axillary artery is negative or inconclusive and the suspicion of large vessel giant cell arteritis is high.

***Panel*: Imaging modalities for the assessment of large vessel giant cell arteritis**

Ultrasonography

Advantages

- Imaging of superficial cranial arteries and part of the large vessels
- Cheap
- No radiation

Disadvantages

- Acquisition of scans operator dependent

Findings at diagnosis and in treated patients with stable remission

- Increased arterial wall thickness (intima-media thickness) at diagnosis that usually persists in treated patients with stable remission
- Hypoechoic appearance of arterial wall with loss of so-called white-black double line (reflecting the normal intima-media complex) is observed at diagnosis; the arterial wall appearance becomes more hyperechoic with absence of the white-black double line in treated patients with stable remission
- Luminal changes might be seen (especially stenosis) at diagnosis, which usually persists in treated patients with stable remission

[^{18}F]fluorodeoxyglucose ([^{18}F]FDG)-PET-CT

Advantages

- Imaging of large vessels and, on new-generation scanners, also cranial arteries
- Can also provide information on alternative diagnoses and polymyalgia rheumatica
- Sensitivity and interpretation affected by uncontrolled diabetes and liver disease; low-dose CT of hybrid [^{18}F]FDG-PET-CT imaging should be used to evaluate the atherosclerosis burden for optimal distinction from active vasculitis

Disadvantages

- Expensive
- Radiation exposure

Findings at diagnosis and in treated patients with stable remission

- Increased [^{18}F]FDG uptake by the arterial wall affected by giant cell arteritis (equal to or higher than liver uptake) at diagnosis; in treated patients with stable remission, there is a gradual decrease of [^{18}F]FDG uptake, although this does not necessarily normalise

Computed tomography angiography (CTA) and magnetic resonance angiography (MRA)

Advantages

- Imaging of large vessels, and for MRA also cranial arteries if combined with 3 Tesla MRI
- Intermediate costs
- MRA does not use radiation

Disadvantages

- Radiation exposure for CTA
- Toxicities related to contrast agent use
- Contraindications for MRA include body metal, claustrophobia, and severe obesity

Findings at diagnosis and in treated patients with stable remission

- Increased arterial wall thickness (intima-media thickness) at diagnosis that usually persists into remission
- Contrast enhancement of arterial wall (mural contrast enhancement) observed at diagnosis, which might decrease in treated patients with stable remission
- Luminal changes might be seen (stenosis or dilation) at diagnosis; dilation often persists or increases in patients with stable remission; stenosis can decrease in patients with stable remission

Imaging can be applied to aid in the assessment of disease activity during treatment monitoring.[54] However, complete resolution of imaging findings is often not obtained despite unequivocal clinical remission. Discrimination between active inflammation and vascular remodelling on imaging is frequently challenging. Thus, imaging findings in treated patients should be interpretated carefully in the overall clinical context of each patient. All imaging modalities are far more useful for the purpose of diagnosing large vessel giant cell arteritis than for the longitudinal monitoring of disease activity.

Ultrasonography

The axillary artery is the main vessel to examine in patients with suspected large vessel giant cell arteritis.[54] Additional large vessels that can be examined include the subclavian, brachial, innominate, carotid, vertebral, femoral, and popliteal arteries. Only parts of the aorta (proximal ascending and abdominal) can be imaged by ultrasonography. If sufficient expertise and time are available, an extended ultrasonographic assessment can provide a small additional diagnostic yield.[6,59] Ultrasonographic scores to quantify the extent of arterial inflammation in temporal and axillary arteries include the Halo count,[61] Halo score,[61] and provisional Outcome Measures in Rheumatology giant cell arteritis ultrasonography score.[62] The application of such scores for diagnosis and treatment monitoring is currently under investigation.

At diagnosis, hypoechoic thickening of the arterial wall can be seen (figure 3A). Thickening mainly represents intimal hyperplasia, whereas the hypoechoic appearance indicates oedema.[63] These changes disrupt the normal white and black line contour of the intima-media complex. The cutoff for intima-media thickness in the axillary artery is 1·0 mm, and cutoff values for other vessels have been reported.[64,65] Unlike in the temporal arteries, arterial wall thickening usually persists in the large vessels when treated patients are in sustained remission.[66,67] Meanwhile

the echogenicity of the arterial walls increases, possibly reflecting the disappearance of oedema and development of fibrosis. Thus, ultrasonography of the axillary arteries aids the diagnosis of large vessel giant cell arteritis, but it does not discriminate well between active inflammation and remodelling during treatment.

MRA and CTA

MRA imaging of the thoracic aorta and its major branches can be combined with high-resolution MRI of the superficial cranial arteries in a single MRI-MRA protocol that takes less than 30 min.[68] The use of gadolinium-based intravenous contrast agents is recommended because these techniques are superior to non-contrast enhanced T2-weighted imaging.[69] CTA is widely available and offers immediate imaging of the aorta and its large branch vessels in routine settings. However, CTA does not assess cranial vessels well.[54]

The typical findings of mural inflammation on MRA and CTA are homogenous and concentric mural thickening and contrast material uptake (figure 3B). Suggested cutoff values for inflamed segments are segments larger than 2·2 mm in the aorta and larger than 1 mm in the subclavian and axillary arteries.[70] Mural thickening and luminal changes often persist during treatment, whereas contrast enhancement can sometimes decrease.[71,72] Luminal changes detected by MRA and CTA include stenosis and dilatation. Dilatation primarily reflects damage, but stenosis could represent active inflammation that can improve after effective treatment.[73]

[^{18}F]FDG-PET-CT

[^{18}F]FDG is a glucose analogue that enables visualisation of tissue-infiltrating macrophages, which have high glycolytic activity. [^{18}F]FDG-PET-CT is a valuable imaging tool for large vessel giant cell arteritis and newer, digital PET systems can also examine cranial vessels.[74] As the only whole-body imaging modality, [^{18}F]FDG-PET-CT might also reveal polymyalgia rheumatica, cancer, and infections. Visual scoring of [^{18}F]FDG uptake at the arterial walls compared with the liver is the preferred method for interpretation of the scans (figure 3C), and these scores can be combined into the total vascular score or PET vascular activity score.[74] These scores gradually decrease during long-term remission, although complete normalisation might not occur.[75,76] A meta-analysis of four studies indicated that [^{18}F]FDG-PET-CT has a sensitivity of 77% and specificity of 71% for discrimination between relapse and remission in patients with large vessel vasculitis.[75] In these four studies, assessment of disease activity was based on clinical assessment with or without angiographic findings, and the [^{18}F]FDG-PET-CT readers were masked to clinical data.

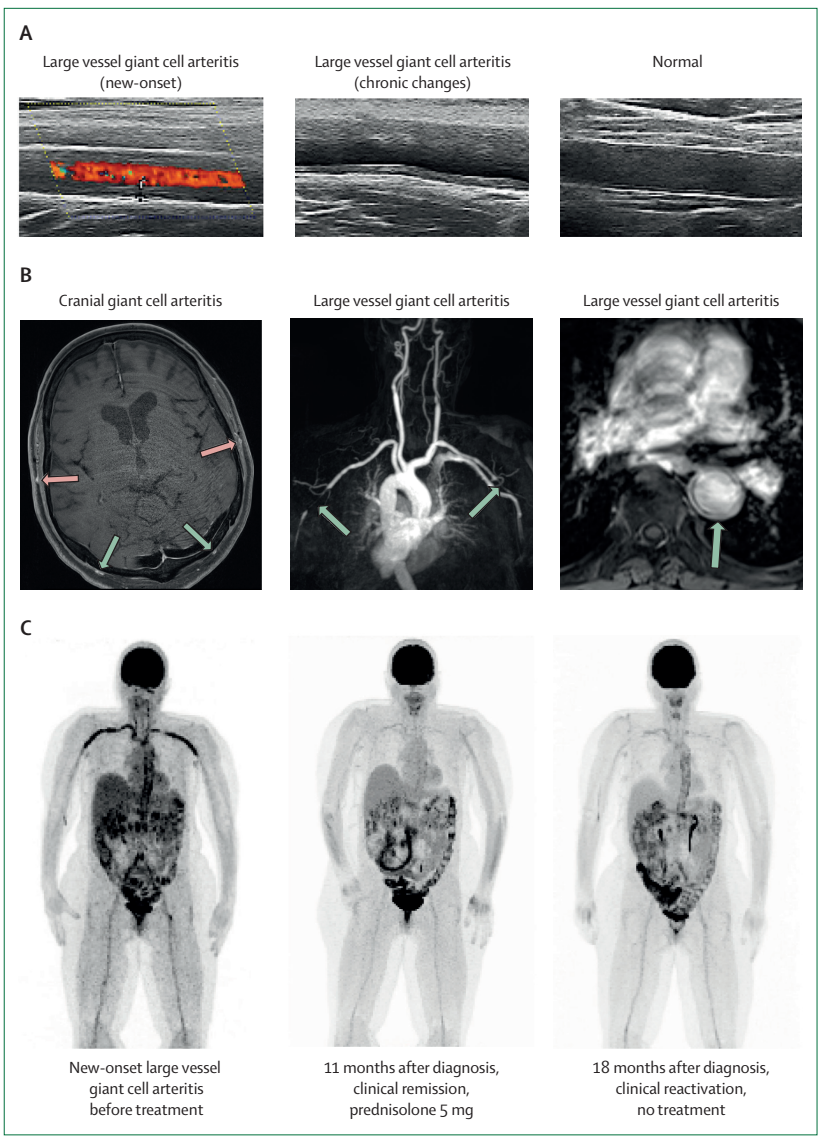

***Figure 3*: Imaging of large vessel giant cell arteritis**
(A) Axillary artery ultrasonography. Left panel: homogenous, hypoechoic thickening of intima-media complex greater than 1·0 mm in a patient with new-onset large vessel giant cell arteritis. Middle panel: persistent, hyperechoic wall thickening in a patient with longstanding disease. Right panel: normal axillary artery. (B) MRI of a patient with mixed cranial giant cell arteritis and large vessel giant cell arteritis. Left panel: high-resolution MRI shows bilateral involvement of the superficial occipital artery (green arrows) and the parietal branch of the superficial temporal artery (red arrows). Middle panel: magnetic resonance angiography displays bilateral inflammatory stenoses of the axillary artery (green arrows). Right panel: transversal T1-weighted MRI shows homogenous concentric thickening of the aortic wall in the descending thoracic aorta greater than 2·2 mm (green arrow). (C) [^{18}F]FDG-PET-CT performed longitudinally in a patient with large vessel giant cell arteritis. Left panel: scan at diagnosis showing pathological [^{18}F]FDG uptake (higher than the liver) in the thoracic and abdominal aorta, and subclavian, axillary, carotid, and iliac arteries. Middle panel: scan during clinical remission showing limited [^{18}F]FDG uptake in the thoracic aorta and subclavian arteries (equal to liver). Right panel: scan during large vessel giant cell arteritis reactivation showing increased [^{18}F]FDG uptake in the aorta and subclavian arteries. [^{18}F]FDG=[^{18}F]fluorodeoxyglucose.

Classification criteria

Classification criteria should not be used for the diagnosis of giant cell arteritis. These criteria do not cover the full spectrum of giant cell arteritis and are mainly intended to distinguish patients with giant cell arteritis from those with other types of vasculitis, rather than patients with conditions that mimic giant cell arteritis. The 1990 ACR criteria for classification of giant cell arteritis were entirely

focused on cranial giant cell arteritis.[4] The ACR and EULAR classification criteria for giant cell arteritis published in 2022 included contemporary imaging techniques as evidence of large vessel giant cell arteritis,[5] thereby offering substantial improvement over the older criteria. Nevertheless, the ACR and EULAR classification criteria still primarily focused on cranial giant cell arteritis: 16 of the 25 points that comprise a potential score are specific for cranial giant cell arteritis, whereas only four of the 25 points are specific for large vessel giant cell arteritis.[5] The ACR and EULAR classification criteria have a sensitivity of 56–62% and specificity of 72–95% for large vessel giant cell arteritis.[5,77]

Treatment

Immunosuppressive treatment

There is no clear cut evidence that patients with large vessel giant cell arteritis should be treated differently to patients with cranial giant cell arteritis. Treatment studies have typically included many patients with mixed large vessel giant cell arteritis and cranial giant cell arteritis and made no systematic attempt to differentiate these subsets rigorously for the purpose of analysing differential treatment responses.[78–80] The application of glucocorticoid treatment and glucocorticoid-sparing therapies, including methotrexate and anti-IL-6 receptor therapy, should follow EULAR recommendations or ACR guidelines.[57,81] A post-hoc analysis of the largest reported trial in giant cell arteritis found no relationship between treatment outcomes and presence of large vessel involvement on imaging.[82] In a retrospective study, the presence of large vessel involvement did not predict relapses after cessation of anti-IL-6 receptor therapy.[83]

Two studies have focused on treatment of large vessel giant cell arteritis. One retrospective study of patients with large vessel giant cell arteritis suggested that mycophenolate mofetil might have glucocorticoid-sparing effects when compared with outcomes reported by other studies.[84] Muratore and colleagues also did a study in which 18 patients with active large vessel giant cell arteritis were treated with three pulses of methylprednisolone followed by subcutaneous anti-IL-6 receptor therapy for 52 weeks without any oral glucocorticoid therapy.[85] This treatment protocol was associated with a relapse-free remission rate of 56% (95% CI 31–78) at 24 weeks and 47% (95% CI 23–72) at 52 weeks. However, four patients who already had aortic dilatation at baseline showed clinically relevant progression of the aortic diameter (defined as an increase in aortic diameter of 5 mm or more) at week 52. Strategies to shorten exposure to glucocorticoid treatment are of keen interest in limited large vessel giant cell arteritis because of their potential to limit glucocorticoid toxicity, but larger randomised trials are needed to test the efficacy and safety of such treatment strategies in a comprehensive manner.

Relapses and treatment requirements

Although multiple studies suggest that large vessel involvement is associated with high relapse rates and long treatment requirements, other studies found no such difference.[2,7] Part of this heterogeneity might be explained by the retrospective nature of the studies, various biases relating to inclusion criteria and loss to follow-up, and differing approaches to the assessment of large vessel giant cell arteritis by imaging. The nature of lesions should also be considered. As an example, stenotic disease in the subclavian artery is associated with more intense treatment requirements than giant cell arteritis causing subclavian artery dilatation.[39] Prospective cohort studies with thorough imaging assessment, protocolised treatment, and lengthy periods of follow-up are needed to determine whether the presence of large vessel giant cell arteritis affects relapse rates and treatment requirements. The optimal duration of therapy for patients with large vessel giant cell arteritis and its effect on quality of life remain to be established.

Damage

Damage to large vessels occurs in a substantial proportion of patients with large vessel giant cell arteritis. One study observed that 41 (39%) of 106 patients with giant cell arteritis developed new angiographic lesions (eg, aneurysm or stenosis) in the aorta or other large vessels during a mean follow-up of 4·4 years.[86] These new lesions were generally identified in patients that already had an angiographic lesion elsewhere at first imaging. The optimal timing and imaging strategy for damage screening in large vessel giant cell arteritis remains uncertain.

The Large Vessel Vasculitis Index of Damage was developed to quantify the accrual of damage in patients with large vessel vasculitis (giant cell arteritis and Takayasu arteritis) and is based on an extensive list of potential complications of large vessel vasculitis.[87] Angiography scores have also been developed that reflect the extent to which stenosis and dilation occur in large vessel vasculitis.[73,88] Both the Large Vessel Vasculitis Index of Damage and the angiography scores require further validation before they are appropriate for use as clinical trial outcome measures.

Aortic damage

Aortic aneurysms and dissections are feared complications of large vessel giant cell arteritis. Such complications primarily occur in the thoracic aorta,[89] and increase the mortality risk of patients with large vessel giant cell arteritis.[90,91] In a prospective study of 40 patients with temporal artery biopsy-proven giant cell arteritis, a dilatation of the thoracic aorta was already noted in six (15%) of 40 patients at diagnosis.[13] Another study showed that 16 (30%) of 54 patients diagnosed by positive temporal artery biopsy eventually developed aortic dilatation during 10-year follow-up.[92] These lesions, determined by contrast-enhanced spiral chest CT, were

most likely to occur within 5 years after diagnosis. One patient died of an aortic dissection. Other studies have reported similar rates of aortic dilatation in the first 5 years after diagnosis of giant cell arteritis.[89]

Progressive aortic dilatation can occur in patients who are in sustained clinical remission. In such patients, it is generally unclear whether progression of the aortic dilatation is the result of persistent, local inflammation, or whether the progressions stem from the enlargement of damaged vascular tissue that is no longer inflamed. Aortic aneurysms removed during surgery might show remodelling rather than active inflammation,[92] but smouldering aortitis can also be present despite an absence of abnormal tracer uptake on pre-surgery [^{18}F]FDG-PET-CT evaluation.[93] PET-CT imaging with immune cell-specific radiotracers could aid decision making in the future by providing direct evidence on the presence or absence of immune cell infiltrates in the aortic wall.[94] It is unclear to what extent glucocorticoid-sparing drugs such as anti-IL-6 receptor therapy mitigate the development of aortic dilatations. Thus, no general recommendations can be given regarding the need for treatment escalation in such patients; decisions regarding the initiation of treatment designed to curb aneurysm progression must be made on a case-by-case basis.[94]

The main risk factor for development of aortic damage is involvement of the aorta. In a study with a mixed retrospective and prospective design, Blockmans and colleagues showed that thoracic aorta involvement on [^{18}F]FDG-PET identified patients prone to the evolution of thoracic aortic dilatation.[95] The same author group observed further support for this finding in a long-term, prospective study.[96] Another report indicated that the presence of dilatations in the subclavian arteries is also strongly associated with the development of aortic aneurysms.[39] A retrospective study suggested that β blockers could reduce the risk of developing new aortic dilatations.[97] Overall, adequate control of blood pressure and other cardiovascular risk factors is crucial for the prevention and management of aortic complications.

Surgical management

For management of the stenotic lesions that could develop in large vessel giant cell arteritis (eg, in the subclavian or axillary artery), the ACR guidelines discourage surgery and other invasive interventions (eg, stents) in favour of the institution of immunosuppressive therapy. The principle behind this recommendation is that collateral circulation in the region of the stenosis might eventually compensate sufficiently for the deficiency of blood flow through the vessel, alleviating limb and organ ischaemia.[57] In contrast, surgery might be required in aortic aneurysms at high risk for dissection and cases of imminent or progressive infarction or damage. If possible, surgery should be targeted for a time when the vasculitis appears to be in remission.[57,81] In patients requiring immediate surgery during active disease, high-dose glucocorticoid treatment at the time of surgery can be considered in consultation with the surgical team.[57]

Search strategy and selection criteria

Two searches were performed of all articles published in English in PubMed, from inception up to the date of the respective search, regarding large vessel vasculitis. The first search was performed on July 21, 2023, using the search terms: ("GCA"[mesh] or GCA [tiab] or temporal arteritis [tiab] or horton [tiab]) AND (large vessel [tiab] or large-vessel [tiab] or large vessel GCA [tiab] or aort* [tiab]) NOT ("Case Reports" [Publication Type] OR case report [tiab]). The second search was performed on July 22, 2023, using the search terms: ("GCA"[mesh] or GCA [tiab] or temporal arteritis [tiab] or horton [tiab]) AND ("Autopsy"[Mesh] or autopsy [tiab] or post-mortem [tiab] or post mortem [tiab]). Articles were also identified through searches of the authors' own files. The final reference list was generated based on originality and relevance to the broad scope of this Series paper.

Concluding remarks and future directives

Large vessel giant cell arteritis constitutes an important and distinctive part of the wider giant cell arteritis and polymyalgia rheumatica spectrum.[2] Appropriate imaging of large vessels should be considered in individuals with suspected giant cell arteritis and polymyalgia rheumatica, because the identification of large vessel giant cell arteritis lesions could alter management plans, affect prognosis, and guide follow-up evaluations. The value of disease stratification regarding the presence or absence of large vessel disease should be further examined in prospective, protocolised cohort studies.[2] Strategies encompassing limited exposure to glucocorticoid treatment and early introduction of glucocorticoid-sparing treatment are appealing for large vessel giant cell arteritis but require further study. The influence of such strategies on the development of aortic complications needs careful attention. In individuals where assessment of large vessel giant cell arteritis disease activity is difficult, molecular imaging methods detecting specific immune cells, such as macrophages and B-cells, could be of future interest.[20,94] Protocols for optimal and efficient monitoring of inflammation and damage in large vessel giant cell arteritis remain to be established.

Contributors

KSMvdG performed the literature search. KSMvdG, TAB, and JRS drafted the figures. All authors were involved in the writing and critical review of the manuscript and approved the final version for publication.

Declaration of interests

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