Role of imaging studies in the diagnosis and follow-up of large-vessel vasculitis: an update

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Imaging studies play a central role in diagnosing and monitoring giant-cell and Takayasu arteritis. Deep, large vessels can be examined by CT or MRI, while colour Doppler ultrasound and MRI have been used with promising results to investigate the temporal arteries. Positron emission tomography is very sensitive in detecting large-vessel inflammation, although it does not delineate the vessel wall. Imaging procedures can also be used to monitor the disease course. However, imaging signs of inflammation may sometimes persist despite clinical remission and, conversely, seemingly unaffected vessels may develop alterations later on.

KEY WORDS: Angiography, MRI, Magnetic resonance angiography, Tomography, X-Ray computed, Ultrasonography, Doppler, Colour, PET, Takayasu arteritis, Giant-cell arteritis.

Introduction

Giant-cell arteritis (GCA) and Takayasu arteritis (TA) are the commonest large-vessel vasculitides (LVV). Imaging studies are increasingly being used to diagnose and to monitor LVV. The aim of this article is to review the literature on imaging studies.

Angiography

Digital subtraction angiography clearly depicts vessel luminal changes and is thus useful in guiding interventional procedures. Panangiography is required to determine the extent of disease involvement [1]. The commonest angiographic findings in TA are long, smooth vascular stenoses and sometimes occlusions and aneurysms [2]. However, angiography cannot demonstrate early vasculitic lesions such as vessel wall alterations and is thus not useful for early diagnosis. In contrast, serial angiograms are helpful in establishing whether new lesions, or worsening of existing lesions, occur over time. Disadvantages of angiography include its invasive nature, the exposition to a significant radiation dose and the risk of ischaemic complications to the iodinated contrast medium [3].

CT and CT angiography

CT demonstrates well the pathological changes of the aorta and of large, deep vessels. CT angiography can evaluate both the vessel wall and the lumen [3] and may thus show vessel wall alterations when the lumen is still unaffected on angiography. However, CT angiography cannot visualize relatively small vessels [4]. Compared with US, CT angiography has lesser resolution, although it clearly differentiates between vascular and perivascular structures [5]. CT carries a small risk because of iodinated contrast administration and of exposure to a large amount of radiation [5, 3].

CT angiography in TA

CT has a role in diagnosing early and advanced TA [6, 7]. In early TA, CT may show arterial wall thickening with mural enhancement and low-attenuation ring on delayed images [5, 7]. On the other hand, in inactive TA the arterial wall is slightly thickened or normal with a high attenuation or calcifications on unenhanced phase images, and absent or only slight mural enhancement without low-attenuation ring on delayed images [1, 7]. In advanced TA, CT shows the typical late-stage complications, including vessel stenosis, occlusion and aneurysm [8].

CT angiography has been shown to accurately reveal large-vessel involvement in a study on 85 TA patients investigated from the carotid to the iliac bifurcation [7]. Of the patients, 95% had aortic involvement with or without aortic branch involvement, while 5% had only aortic branch involvement. The left common carotid artery (77%) and the left subclavian artery (76%) were most commonly involved. Extent of disease involvement assessed by mural change was wider than that assessed by luminal change in 61% of the patients. Arterial involvement was contiguous in 81% of the patients. Active and inactive lesions coexisted in 11% of the patients.

Compared with conventional angiography, CT angiography has been shown to accurately assess stenotic lesions in all brachiocephalic trunks, in 37 of 40 common carotid arteries and in 33 of 40 subclavian arteries examined, with a sensitivity and specificity of 93 and 98%, respectively [9].

Compared with B-mode ultrasonography (US), electron-beam CT has been demonstrated in a study to be able to identify long, homogeneous, circumferential thickening in 98% of the patients (vs 71% by US) [10]. Stenoses were detected by US and electron-beam CT in 44 and 32% of the patients, and aneurysms in 0.4 and 68%. Thirty-seven per cent of the patients had pulmonary artery abnormalities on electron-beam CT.

CT angiography has also been proposed to evaluate disease activity. In a study, all six Takayasu patients with active disease showed wall enhancement, although CT angiography failed to show enhancement in further two patients with active disease [11]. However, wall enhancement was not demonstrated in another study in either active or inactive patients [8].

Finally, CT angiography may have a role in monitoring the disease course. Aortic wall enhancement was shown to resolve after immunosuppressive therapy in 7 of 13 Takayasu patients [12]. Wall thickening decreased after immunosuppressive therapy in 56% of the lesions, albeit 25% of the initial lesions showed evidence of progression. In contrast, another study [8] failed to show a reduction in wall thickening of the supra-aortic branches after glucocorticoid therapy, possibly due to the limited sensitivity of CT angiography in depicting lesions in arteries smaller than the aorta.

MRI and magnetic resonance angiography

MRI provides multiplanar sectional images without using ionizing radiation [1]. Vessel wall oedema on T2-sequences and mural
contrast enhancement on T1-sequences are early signs of inflammation [13], although they may also reflect hypervascularity [14]. Increased vessel wall thickness on T1-weighted sequences, usually with a diffuse, circumferential pattern, is another sign of early vasculitis [14].

MR angiography (MRA) is used to visualize the vessel lumen [3]. Limitations of MRA include poor visualization of calcifications, misinterpretation of vascular branch-points as occlusions and falsely accentuated stenoses [1, 3].

Disadvantages of MRI include poor visualization of small vessels and the high costs of the procedure [3].

**MRI in TA**

The diagnostic accuracy of contrast-enhanced 1.5T MRA has been evaluated in 30 patients with suspected TA, conventional angiography being the comparator [15]. TA was diagnosed in 20 patients. MRA depicted vascular lesions in the aorta and its major branches in 100% and in the pulmonary arteries in 50% of patients. MRI accurately depicted 98% of 330 arteries, but 7 stenotic arteries were overestimated as occluded. The sensitivity and specificity of MRI for the diagnosis of TA were both 100% [15].

MRI has also been used to determine disease activity. In a series of 24 patients, active disease was characterized by increased vessel wall thickness compared with inactive disease [16]. In addition, 94% of patients with active TA had evidence of oedema of at least one vessel segment [16]. However, vessel wall oedema could also be demonstrated by MRI in 56% of patients considered to be in clinical remission. The presence of oedema did not consistently correlate with the development of new lesions since 6 of 16 patients followed up had no disease progression despite persistent vessel wall oedema, while three patients developed new lesions at sites without oedema.

The effects of immunosuppression on MRI/MRA findings have been investigated in a limited number of cases. In three TA patients, vessel wall thickness and oedema on MRI improved in all [17], while in four other patients contrast enhancement resolved following immunosuppressive therapy [18].

**MRI in GCA**

MRI has been used in GCA to evaluate both the temporal arteries and the large vessels. Bley et al. [19] investigated 20 patients with suspected GCA with a 1.5T scanner. Mural thickness and contrast enhancement, and lumen diameter of the temporal arteries were evaluated. Sixteen patients underwent a temporal artery biopsy, and 17 fulfilled the ACR criteria for GCA. Of the 17 patients with a final diagnosis of GCA, 16 had true-positive and one had false-negative MRI findings. The three patients who did not fulfill the ACR criteria had true-negative MRI findings. Thirteen of 15 biopsied patients had true-positive findings and two false-negative findings. These results thus demonstrate that MRI findings agreed well with histological results and with the fulfillment of the ACR criteria. Similarly, active inflammation could be demonstrated using high-resolution contrast-enhanced 3T MRI in the temporal arteries of eight of nine GCA patients [20]. In the patient without temporal artery involvement, MRI documented inflammation of the occipital arteries.

We investigated by contrast-enhanced 1T MRI the temporal arteries of 24 untreated patients with suspected GCA [21]. Temporal artery clinical inspection, colour Doppler (CD) US and biopsy were performed. Thirteen patients met the 1990 ACR classification criteria for GCA, nine of whom had a positive biopsy. Marked mural enhancement was observed in 3 of these 13 patients and a halo on CDUS in 9. Ten patients had abnormal temporal arteries on examination. The sensitivity and specificity of MRI mural enhancement for the diagnosis of GCA according to the ACR criteria were 27.5 and 100%, respectively, compared with 69 and 100% using CDUS and 76.9 and 100% by clinical assessment.

Taken together, these data suggest that 1.5T–3T MRI is much more sensitive for diagnosing GCA than 1T MRI. The coils used can also affect the quality of the MRI images. If these results that stem mainly from one research group [19, 20] were replicated, high-resolution MRI could be recommended as a valuable adjunct in diagnosing GCA. In particular, MRI could be useful in those patients in whom cranial vessels other than, or in addition to the temporal arteries (such as the occipital arteries) are affected [20].

There is limited knowledge on the role of MRI in the follow-up of GCA patients. In a patient, marked improvement of MRI inflammatory changes of the temporal arteries was observed 8 weeks after commencing glucocorticoid therapy [22]. In another case, mural enhancement and vessel wall thickening resolved 15 months after treatment with glucocorticoids and methotrexate [19].

MRA/MRI has also been used to diagnose large vessel involvement in GCA with encouraging preliminary results [23].

**Ultrasonography**

US transducers have a resolution of ~0.1 mm [24], which is 10-fold better than MRI [5]. CDUS, which combines imaging with flow-velocity determination, can assess both vessel anatomy and luminal status and may demonstrate early vessel wall alterations before detectable lumen changes on angiography [5, 25]. Other advantages of CDUS include its limited cost, the relatively short time required and the absence of radiation [5].

US shows different patterns in vasculitis and atherosclerosis [26–29]. In normal subjects, the carotid artery wall shows two parallel, echogenic lines separated by a relatively hypoechoic space representing the lumen-intima and the media-adventitia interface, respectively [27]. The space in between is commonly referred to as the intima–media complex (IMC) [29].

In patients with LVV, increased diffuse, circumferential IMC thickness in transverse sections (dubbed ‘macaroni sign’) is thought to reflect inflammatory oedema, increased vascularity or both. In contrast, atherosclerotic lesions are usually characterized by a localized thick IMC pattern [29]. Atherosclerotic and vasculitic lesions can also be distinguished, at least to some extent, on the basis of the vascular segments involved [30] (Table 1).

US has a number of limitations. It is quite operator dependent and cannot image well some arterial segments, such as the left proximal subclavian artery and the thoracic aorta because of overlying structures [5], while abdominal vessel may be obscured by bowel gases and fat [3].

**Doppler US in TA**

In patients with TA, increased IMC thickness relative to controls has been reported [29]. In a study, 46 carotid arteries of 23 Takayasu patients were scanned by B-mode US [29]. In 34 carotid arteries, the IMC was diffusely thickened (bilaterally in 79% of the patients), while only one carotid artery showed localized IMC thickening. Other abnormalities included occlusion and
dilatation. Altogether, abnormal findings on US were noted in 83% of the common carotid arteries (CCAs), whereas only 39% of the CCA showed angiographically detectable alterations. CCA involvement with sparing of the internal and external carotid arteries is frequent in TA [31]. Involved CCA show diffuse or circumferential thickening of the vessel wall, which is significantly thicker in active than in inactive lesions, while hyperechogenecity has been observed in both active and inactive disease [31]. An example of a CDUS scan of the CCA of a patient with TA is shown in Fig. 1A, together with a CT angiography scan (Fig. 1B) of the same vessel.

Serial CDUS studies, instead of repeat angiographies, may theoretically be used to monitor patients [32]. A study showed progression of circumferential thickening, but no longitudinal spread of vascular lesions in two out of six patients with TA [33].

Doppler US in GCA

High-resolution CDUS can depict both the vessel wall and the lumen of the temporal arteries. Schmidt et al. demonstrated that the most specific (almost 100% specificity) and sensitive (73% sensitivity) sign for GCA was a concentric hypoechogetic mural thickening, dubbed ‘halo’, which the authors interpreted as vessel wall oedema [34]. Examples of ‘halo’ are shown in Figs 1 and 2. In contrast, stenoses and occlusions, although common (80% of cases), were less sensitive and specific for GCA. Since then, numerous contributions have been published on the diagnostic value of CDUS. In a study from our group, a hypoechoic halo around the temporal artery lumen had a specificity of 79% but a sensitivity of only 40% for the diagnosis of biopsy-proven GCA [35]. Subsequent studies have confirmed the high specificity but lower (40-90%) sensitivity of the halo for GCA, with more recent studies reporting higher sensitivity values, perhaps reflecting improvement in the equipment, increased familiarity of the ultrasonographers with the procedure or both. Recently, the diagnostic value of CDUS in GCA has been reviewed in a meta-analysis [36] that included all studies published until 2004 enrolling ≥5 patients and using biopsy or the ACR criteria as reference standard. The weighted sensitivity and specificity of the halo sign were 69 and 82%, respectively, compared with biopsy and 55 and 94%, respectively, compared with ACR criteria. Stenosis or occlusion was an almost equally sensitive marker compared with biopsy (sensitivity 68%) or ACR criteria (sensitivity 66%). Between-study heterogeneity was significant. These data confirm that the sensitivity of CDUS for GCA is still somehow lower than specificity. Therefore, while a positive halo sign strongly supports a diagnosis of GCA in the presence of compatible clinical manifestations, the absence of a halo does not rule it out. One study showed that the presence of bilateral halos around the temporal arteries had a 100% specificity for the diagnosis of GCA [37], although these findings should be replicated before the bilateral halo sign might gain acceptance as a diagnostic substitutive for a temporal artery biopsy.

18F-fluorodeoxyglucose PET

Increased glucose uptake by active cells can be detected by administration of a fluorine-labelled glucose analogon
Role of $^{18}$FDG PET scan in the diagnosis of patients with large-vessel arteritis

PET has a role in diagnosing early LVV by revealing inflammatory cell infiltration of the vessel wall, one of the earliest events in arteritis [43]. In five patients with early, clinically active TA, elevated FDG uptake was noted in all patients and in 76% of vascular segments [44]. In contrast, MRI vessel wall abnormalities (thickening and contrast enhancement) were observed only in 32% of the vascular regions scanned and no abnormalities could be detected using contrast-enhanced MRA [44]. Similarly, in another study on 18 patients with suspected TA (16 of whom fulfilled the ACR criteria), PET correctly identified 11 out of 12 patients with active TA and all 6 patients with inactive disease, achieving a sensitivity of 92% and a specificity of 100% [47]. In a few cases with active disease, PET scan was positive despite normal inflammatory markers.

In a large series of 35 GCA patients, PET was performed before glucocorticoid therapy and at 3 and 6 months if the initial scan was positive [48]. A score based on intensity and extent of FDG uptake was calculated. At diagnosis, vascular uptake was noted in 29 patients (83%), mainly in the subclavian arteries (74%), but also in the aorta (>50%) and up to the femoral arteries (37%). The score decreased significantly at 3 months but not further at 6 months. No correlation was found between score decrease and the risk of clinical relapse. In another study, abnormal vascular uptake consistent with arteritis could be demonstrated by PET in four of five PMR patients with a normal temporal artery biopsy [49], whereas a more recent paper by the same authors reported abnormal vascular uptake (but less intense than that seen in GCA) in 31% of PMR patients without clinico-histological evidence of GCA [50].

Chronic periaortitis (CP) is a rare condition characterized by spreading of fibro-inflammatory tissue from the aorta into the retroperitoneum that can present as idiopathic retroperitoneal fibrosis (IRF), inflammatory abdominal aortic aneurysms and periuinteumal retroperitoneal fibrosis [51]. In a study from our group, PET scan was performed in 7 untreated patients with CP diagnosed with CT and in 14 neoplastic controls [52]. All patients had grade 2–3 vascular uptake in the abdominal aorta and/or iliac artery, whereas no controls showed vascular uptake >1+. Vascular uptake in abdominal aorta and/or iliac artery and thoracic aorta and/or its branches was seen in 100 and 43% of CP patients, respectively, but in none of the controls. These findings suggest a vasculitic nature of CP.

Role of $^{18}$FDG PET scan in the follow-up of patients with large-vessel arteritis

PET has been reported to identify vessel segments with active disease that subsequently progressed to stenosis [53], although not to specifically predict which affected segments would eventually become stenotic. Conversely, PET findings appear to normalize after immunosuppressive treatment. In a study, PET scans of 30 involved arterial regions showed uptake normalization in 24 regions after immunosuppression, paralleling clinical and laboratory improvement [43]. In contrast, a decrease in vessel wall thickness on MRI was observed in only 2 out of 17 involved segments.

In four patients with LVV, glucocorticoid therapy led to clinical and laboratory improvement and significantly reduced tracer uptake in all patients, while the number of involved segments decreased from 28 to 15 [54].

In a study comparing PET findings with angiography, MRA and clinical parameters, PET was performed in five untreated patients with active TA or GCA and after treatment-induced remission [55]. PET was positive in all patients, FDG uptake clearly decreased compared with baseline in all patients in remission. In eight arteries of four patients, only PET showed disease involvement, while in five arteries of two patients only angiography or MRA showed involvement [55]. Andrews et al. [18] compared PET and MRI in the assessment of disease activity after immunosuppression in six TA patients. The $^{18}$FDG vessel wall uptake was judged to be much more reliable in defining disease activity than gadolinium enhancement on MRI.

There are limited data on the use of PET in the follow-up of CP patients [51]. In a patient with IRF, reduction of the fibro-inflammatory tissue on MRI following immunosuppression was paralleled by virtual normalization of inflammatory markers and PET findings [56]. A clinical relapse was reliably detected by PET in the absence of an elevation of the inflammatory markers. Conversely, in seven patients with IRF, following immunosuppressive therapy PET findings normalized in all but one patient, whereas CT showed a residual mass in all patients, probably representing metabolically inactive tissue [57]. Taken together, these data may suggest that PET could be more sensitive and specific than inflammatory markers and CT in evaluating disease activity in CP, but further studies are required to confirm these preliminary results.

Limitations of PET

PET does not convey information regarding wall structure or luminal flow [5]. Vascular uptake on PET is not specific for vasculitis. In a retrospective analysis of 137 patients who underwent PET scan for various reasons, older patients showed increased vascular FDG uptake [58], probably related to age-related vessel changes, including atherosclerosis [58]. Discriminating between atherosclerotic and vasculitic lesions may be challenging, but a number of characteristics may point towards one condition and away from the other (Table 1 and Fig. 3). First, vasculitic lesions are usually characterized by a more intense FDG uptake [5, 41]. Second, involvement of vessels usually spared by atherosclerosis would point to vasculitis. Third, atherosclerotic plaques show as ‘hot spots’, whereas vasculitic lesions are usually smooth-linear [59]. In doubtful cases, the involved vessels should be imaged by US or MRI. Practical limitations of PET include its high costs and restricted availability.

Indications for the use of PET in large-vessel vasculitis

PET has an important role in the diagnosis and follow-up of TA. It is also useful in patients with systemic complaints and...
unexplained inflammation [24, 60]. In patients with fever of unknown origin, PET scan serves well in identifying underlying LVV [61, 62], infections and tumours [39, 40].

Concluding remarks

LVV often pose diagnostic challenges because they can present with a panoply of manifestations. Imaging studies can assist in diagnosing early vasculitis by demonstrating vessel lesions even when angiography is negative. Imaging procedures are also useful for monitoring purposes. Signs such as increased vessel wall thickness, a halo on US or vessel wall oedema and mural enhancement on CT or MRI, are usually considered evidence of active disease. However, not every vessel with active disease on imaging will develop structural changes and, conversely, unaffected vessels may develop alterations [5, 16]. Second, inflammatory changes on imaging may persist despite clinical remission [16]. Vessel wall thickness usually gradually decreases as inflammation subsides [31], but it is difficult to confidently discriminate between active inflammatory from chronic fibrotic lesions on the basis of vessel wall thickness alone [63]. Vessel stenosis may be due to active vasculitis, but also to scarring after inflammation has abated [5, 31]. PET may be a more reliable procedure in the evaluation of disease activity [38].

A thorough knowledge of the possibilities and limits of the various imaging procedures places the clinician in the best position not only to diagnose early vasculitis, but also to fine-tune the treatment to the requirement of the individual cases.

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