**Dossier thématique**

**Diagnosis and extension of giant cell arteritis. Contribution of imaging techniques**

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**Points essentiels**

**Diagnostic et extension des artérites à cellules géantes. Apport de l’imagerie**

La biopsie chirurgicale de l’artère temporale reste la façon la plus directe de diagnostiquer une maladie de Horton. Pourtant, la biopsie n’est pas positive dans 100 % des cas, même pas chez les patients atteints de symptômes purement crâniaux. Ici, la tomographie par émission de positons peut venir en aide. Cette technique nucléaire a démontré que la maladie de Horton touche les grands vaisseaux comme l’aorte ou les artères subclavières dans 50 à 80 % des cas. L’ultrasonographie de l’artère temporale touchée par l’inflammation peut révéler un halo, correspondant à un œdème intimal. Confiée à des praticiens très expérimentés, l’ultrasonographie peut remplacer la biopsie chirurgicale. Imagier par résonance magnétique et la tomodensitométrie ne sont pas employés pour diagnostiquer la maladie de Horton, mais ces techniques peuvent visualiser une atteinte de l’aorte avec une aortite ou une inflammation d’une artère particulière.

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**Key points**

Performing a temporal artery biopsy is still the easiest way to diagnose giant cell arteritis. However, this biopsy is not always positive, even not in patients with prominent cranial symptoms. In these cases, positron emission tomography with 18-fluorodeoxyglucose as a tracer is a valid alternative. This nuclear technique has demonstrated that involvement of large arteries such as the aorta or the subclavian arteries occurs in 50 to 80% of patients.

Ultrasonographic examination of an inflamed temporal artery can demonstrate a “halo”, corresponding to edema of the intimal layer of the artery. Only in very experienced hands, this non-invasive technique can replace a surgical biopsy.

Magnetic resonance imaging and computerized tomographic scanning are not used in the diagnosis of giant cell arteritis, but these techniques can visualize the extent of the disease, e.g. to the aorta with possible aortitis or to a partial artery.

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When an elderly patient presents with typical complaints of giant cell arteritis (GCA) such as headache, visual disturbances, jaw claudication, and when he has a high sedimentation rate on a blood examination, a temporal artery biopsy may reveal the diagnosis without further delay. However, this typical picture is not always present, and sometimes patients with GCA present with vague symptoms such as fever or weight loss or may even be asymptomatic and have only an unexplained rise of sedimentation rate and C-reactive protein.
In these patients, GCA is only one of several possibilities, and a temporal artery biopsy will not be performed at the first line. Moreover, even in typical GCA cases, temporal artery biopsy is not always positive. With jaw claudication (present in 34% of patients), diplopia (present in only 9% of GCA patients), and a beaded or enlarged temporal artery being the strongest predictors of a positive temporal biopsy [1], the negative predictive value of a temporal artery biopsy taken in ideal circumstances is only in the range of 90% [2]. In 1999, Brack et al. described a variant of GCA, which is characterized by involvement of the great vessels and a higher likelihood of sparing the temporal arteries; in these patients the sensitivity of temporal artery biopsy was only 58% [3]. In patients with Takayasu arteritis or chronic periaortitis, we have no easily attainable inflamed blood vessel to biopsy. Diagnosis of Takayasu’s disease was usually made by classic angiography, which is an invasive technique and which can only detect late stages of the disease, when stenoses or aneurysms have already occurred. In recent years, new diagnostic methods such as ultrasonography, fluorodeoxyglucose positron emission tomography (FDG-PET), CT-scan and magnetic resonance imaging (MRI) are increasingly used to diagnose large-vessel vasculitis. This has lead to the understanding that extracranial involvement of GCA is not so anecdotal as previously thought, but occurs rather frequently, albeit mostly at a subclinical level.

**Fluorodeoxyglucose positron emission tomography**

The discovery that FDG-PET can reveal the presence of large-vessel vasculitis was made accidentally in 1996, by comparing FDG-PET scintigraphy to Gallium scintigraphy in patients with fever of unknown origin (FUO) [4]. Until then, whole body scintigraphy using Gallium-67 citrate was routinely performed to look for a source of the fever-producing disease. FDG-PET imaging use in internal medicine was limited to evaluation of oncologic processes, especially lymphomas and lung tumours. We hypothesized that F-18 FDG would be a good isotope to visualize inflammation as well and therefore organized a prospective study in which patients fulfilling the criteria for FUO would undergo both Gallium scanning and FDG-PET scintigraphy. Some patients with longstanding fever but no other firm clues for any particular disease were shown to have clearly increased FDG-uptake in their large thoracic vessels (figure 1). In the subsequent work-up of these patients, which included a temporal artery biopsy if they were older than 50 years, the diagnosis was proven to be GCA.

In 1999, we published our experience with FDG-PET in a preliminary series of 5 patients with what was considered as isolated polymyalgia rheumatica (PMR), 6 patients with GCA and 23 age-matched control patients with other inflammatory conditions [5]. Vascular FDG-uptake in the thoracic vessels and in the arteries of the upper legs was seen significantly more in the GCA and PMR patients than in the controls. FDG-uptake in the thoracic vessels was found to be very specific for GCA and/or PMR since it was encountered in only 1 control compared to 8 of 11 patients. The temporal arteries themselves could not be visualized by this technique. This was due to their small diameter (individual vessels need to be more than 4 mm in diameter to be visualized), their superficial position (there is a false-positive signal at the transition from body to air) and the close vicinity of the glucose-consuming brain. In 4 patients,

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**Glossary**

FDG-PET | fluorodeoxyglucose positron emission tomography
FUO | fever of unknown origin
GCA | giant cell arteritis
MRA | magnetic resonance angiography
MRI | magnetic resonance imaging
PMR | polymyalgia rheumatic
TVS | total vascular score
FDG-PET scan was repeated during steroid treatment and at a time when all symptoms had disappeared and inflammatory parameters had normalized. Vascular FDG-uptake had clearly decreased with treatment. It is felt that some of the patients who were considered to have isolated PMR (since they had a normal temporal artery biopsy and no typical signs of GCA such as visual disturbances, jaw claudication or headache) and had very intense vascular inflammation, were in fact suffering from non-cranial large-vessel vasculitis, a condition not well recognized at that time [3].

A larger series on the use of FDG-PET scintigraphy in patients with GCA and/or PMR (n = 25, of whom 13 had histological evidence of vasculitis in the temporal artery and 44 age-matched control patients was published in 2000 [6]. Thoracic vascular FDG-uptake had a sensitivity of 56%, a specificity of 98%, a prospective predictive value of 93% and a negative predictive value of 80% for the diagnosis of GCA/PMR (which was considered as one condition). Vascular FDG-uptake in the legs had a slightly higher sensitivity (64%) but a lower specificity (77%). The highest yields were obtained in patients with predominant systemic symptoms, such as fever, weight loss or general malaise. Although vascular FDG-uptake in the legs is less specific (probably due to atherosclerosis, which is more abundant in the lower limbs), striking PET-images on the involvement of these arteries in 4 patients with rapidly progressive claudication of the lower limbs due to extracranial GCA, were reported by Tato and Hoffmann [7].

In 2004, Brodman et al. reported on a series of 22 consecutive GCA patients undergoing FDG-PET scintigraphy and duplex ultrasound [8]. All patients had a hypoechoic halo around the temporal arteries, the large arteries or both in duplex ultrasound. Temporal artery biopsies were not routinely performed (only 8 of 22). As judged by duplex ultrasound, six patients had GCA involving both the large arteries and the temporal arteries, five patients showed a halo only in the large arteries without concomitant involvement of the temporal arteries, and 11 patients showed only involvement of the temporal arteries. All patients with a halo sign in the aorta, subclavian, axillary, and iliac arteries, also showed elevated FDG-uptake in the same vessels, with complete agreement in the anatomic distribution of the vasculitis. When the echographic halo sign was only detected in the temporal arteries, FDG-PET was completely negative in the temporal arteries as well as all other arterial locations. This confirms the fact that FDG-PET is not suitable for the assessment of pathology in the temporal arteries, for reasons explained above.

In 2006, we published a prospective study on the value of FDG-PET scintigraphy in the diagnosis and follow-up of 35 biopsy-proven GCA patients [9]. PET-scans were performed before the start of therapy, at 3 months treatment and at 6 months treatment. We hypothesized that patients with significant decreases of vascular FDG-uptake after 3 and 6 months of steroid therapy would be at lower risk of relapse, but this was not the case. Vascular FDG-uptake was noted at diagnosis in 83% of patients, especially in the subclavian arteries (74%), but also in the thoracic and abdominal aorta (> 50%) down to the femoral arteries (37%). To quantify the extent of the disease, a total vascular score (TVS) was calculated, ranging from 0 to 21 based on the intensity of FDG-uptake (graded from 0 to 3) in seven vascular beds (thoracic aorta, abdominal aorta, subclavian arteries, axillary arteries, carotid arteries, iliac arteries and femoral arteries). The mean TVS at diagnosis was 6.0 ± 6.2, 8 patients had a score > 11 and one patient had the maximal score of 21. FDG-uptake decreased substantially from diagnosis to 3 months of therapy, paralleling inflammation parameters, but there was no further decrease at 6 months. One possible explanation for this late perpetuating FDG-uptake might be vascular remodelling. There was a strong relationship between the presence of PMR symptoms in GCA patients and FDG-uptake in the shoulders but not between PMR symptoms and inflammation of the subclavian or axillary arteries. This fits with the view that PMR symptoms are caused by perisynovitis of the shoulders. We concluded that finding vascular FDG-uptake is a sensitive marker for large-vessel vasculitis and that GCA involves arteries far beyond the temporal arteries. There is no role for serial PET-scans in the follow-up of GCA patients, since such scans cannot discriminate as to which patients will relapse (and therefore need higher or longer steroid therapy).

In a study on 25 GCA patients who presented with a complicated disease course despite immunosuppressive therapy, PET was judged unreliable for assessing large-vessel inflammation, which probably is due to the confounding effect of previous steroid administration [10]. In untreated patients with atypical presentations of GCA, such as weight loss, fever, malaise, and arm claudication, and in whom the vasculitis probably does not involve the temporal arteries, FDG-PET is the diagnostic technique of choice. This was also the conclusion of a retrospective study of 11 GCA patients with highly variable clinical presentations [11].

In a paper from 2008, Hautzel et al. introduced a receiver operating characteristic-based cut-off ratio for the assessment of large-vessel involvement in GCA with FDG-PET. The ratio between the FDG-uptake in the aortic wall and FDG-uptake in the liver is calculated, which offers a more quantitative interpretation of PET results [12]. Future comparative studies between both methods are needed to determine if this semi-quantitative approach is more suitable for the clinical management of GCA patients.

In a recent meta-analysis of six (badly selected) studies on the diagnostic use of FDG-PET in GCA, Besson et al. reported a calculated sensitivity of 0.80, a specificity of 0.89, a positive predictive value of 0.85 and a negative predictive value of 0.88 [13]. However, many studies on the use of PET in GCA are hard to interpret since only a minority of patients are biopsy-proven,
there is no clear distinction made between GCA, isolated PMR and Takayasu arteritis and PET scintigraphies are not performed at diagnosis, before the start of treatment, but during steroid treatment or at a relapse.

Reviewing 32 studies including 604 patients with large-vessel vasculitis, Treglia et al. concluded that FDG-PET is a useful imaging method in the initial diagnosis and in the assessment of activity and extent of the disease but that its usefulness in evaluating treatment response, remains unclear [14].

In a study on 46 biopsy-proven GCA patients who all underwent FDG-PET scintigraphy at the time of diagnosis and before the start of steroids, we investigated whether there was a correlation between the extent of vascular FDG-uptake during the acute phase of GCA and the aortic diameter at late follow-up. All patients underwent a CT-scan of the aorta a mean of 47 ± 30 months after the initial diagnosis. The diameter of the aorta was measured at six different levels (ascending aorta, aortic arch, descending aorta, abdominal suprarenal, juxtaarenal and infrarenal aorta) and the volumes of the thoracic and of the abdominal aorta were calculated. Patients who had increased FDG-uptake in the aorta at diagnosis of GCA, had a significantly larger diameter of the ascending aorta ($P = 0.025$) and descending aorta ($P = 0.044$) as well as a significantly larger volume of the thoracic aorta ($P = 0.029$). In multivariate analysis, FDG-uptake at the thoracic aorta was the only parameter which was associated with late volume of the thoracic aorta ($P = 0.039$). These findings might indicate that FDG-PET scintigraphy not only has a place in the diagnosis of atypical cases of GCA, but also has a prognostic value for aortic dilatation [15].

In conclusion, studies on FDG-PET scintigraphy have demonstrated that in GCA, widespread involvement by the vasculitic process of large arteries throughout the body occurs much more frequently than originally thought. For those patients in whom the temporal biopsy is negative or for those with atypical clinical pictures in whom GCA is only one of several possibilities, FDG-PET scan—although expensive and not available everywhere—is a logical alternative approach. For large-vessel GCA not involving the temporal arteries, it is probably the examination of choice as a single examination that shows vascular involvement throughout the body. Although FDG-PET seems to be a very specific technique to visualize large-vessel inflammation, one should only rely on very clear pictures in order to distinguish from physiologic uptake or atherosclerosis. There is no need to repeat FDG-PET studies during treatment: clinical assessment and biochemical monitoring of C-reactive protein concentrations are reliable and less costly. If there is still concern that a patient is relapsing at a certain time point, a new FDG-PET scan may be considered, as one of several parameters taken into account in the decision whether to restart/increase or not steroid treatment.

Color duplex ultrasonography
Schmidt et al. were the first to use duplex ultrasonography to examine temporal arteries in patients with GCA. In 22 out of 30 patients (73%) with known GCA, they found a hypoechoic halo in the temporal arteries, a finding that the investigators attributed to inflammation-associated edema of the vessel wall [16]. This halo sign was not found in 82 control patients (of whom 37 had PMR), suggesting that the finding was very specific for GCA.

In a blinded ultrasound study on 86 consecutive patients suspected of GCA or PMR, a hypoechoic halo had a sensitivity for biopsy-proven GCA of only 40% and a specificity of 79%, which was no better than finding an abnormal temporal artery on clinical examination [17]. In a meta-analysis of 23 studies, temporal artery duplex ultrasonography was found to have a pooled sensitivity of 87% and a specificity of 96% compared with the clinical diagnosis [18]. In a second meta-analysis in which only 8 studies who fulfilled technical quality criteria for ultrasound were included, unilateral halo sign achieved an overall sensitivity of 68% and specificity of 91%. Bilateral halo signs had a sensitivity of 43% and a specificity of 100% [19]. Some groups continue to report very low sensitivities for the halo sign, even as low as 10%, reflecting probably the high level of operator dependency [20]. Unless done by very experienced hands, ultrasound cannot replace temporal artery biopsy. Another drawback of ultrasonography is its inability to depict structures below bone and air. Hence, it provides little information on the thoracic aorta. The axillary arteries however are easily and quickly accessible with ultrasound; as in the temporal arteries, the wall swelling is hypoechoic in untreated active disease and decreases within months or years in most cases [21]. Combining ultrasound examination of the axillary arteries to that of the temporal arteries, increases its diagnostic yield in large-vessel GCA. Compared to the axillary arteries, the subclavian arteries and proximal brachial arteries were less often involved [22].

Computerized tomography angiography
From retrospective studies, it is known that GCA carries an increased risk of aortic aneurysm formation and dissection, particularly in the thoracic aorta [23–25]. Therefore, a yearly follow-up of GCA patients with an X-ray of the thorax and an abdominal ultrasound or a yearly CT-scan of the aorta (without contrast administration) are reasonable. But also at the time of diagnosis already, CT-scan can be used to demonstrate aortic involvement. In a prospective controlled study, Agard C et al. compared helical aortic CT-scans of 22 biopsy-proven GCA patients during the 4-week period following diagnosis to 22 age, sex and cardiovascular risk factors matched controls. Thickening of the aortic wall was more frequent among patients than controls (45.4% versus 13.6%, $P = 0.02$). Aortic thickening (mean 3.3 mm) was located in the ascending part
of the thoracic aorta in 22.7% of the patients and in the abdominal aortic wall in 27.3% of the patients, with no evidence of thickening at these levels in the controls \( (P = 0.05, P = 0.02 \text{ respectively}) \). Hence, the authors concluded that inflammatory aortic thickening–aortitis–occurs frequently at the time of diagnosis of GCA [26]. In another prospective study, CT angiography was performed in 40 consecutive patients with newly-diagnosed biopsy-proven GCA. Aortitis was defined as circumferential aortic wall thickness of 2 mm or more with or without contrast enhancement of the vessel wall observed in zones without adjacent atheroma, arteritis of the other vessels was considered to be present when the thickness of the artery wall was 1 mm or more. The aorta (especially in the descending part, the aortic arch and the abdominal aorta, less frequent in the ascending aorta) was involved in 65% of patients, its main tributaries in 57.5% (the brachiocephalic trunk in 47.5%, the carotid arteries in 35%, the subclavian arteries in 42.5%, the axillary arteries in 17.5%, the splanchnic arteries in 22.5%, the renal arteries in 7.5%, the iliac arteries in 15% and the femoral arteries in 30% of patients) (figure 2). Dilation of the thoracic aorta – mainly in the ascending part – was already present at diagnosis in 15% of patients [27]. Late aortic dilation also occurs predominantly at the ascending aorta, while this level seems less inflamed at the time of diagnosis. This difference can be explained if we consider the inflamed descending aorta, being more stiff, as a functional coarctation, rendering the ascending aorta, subjected to high pressure, prone to progressive dilation [27].

**Figure 2**

Increased thickness of the descending aortic wall with peripheral contrast enhancement in patient with giant cell arteritis (arrow) Courtesy of Dr. Maria Cid.

**Magnetic resonance imaging**

Diagnostic criteria for inflamed vessel segments are thickening of the wall and increased mural Gadolinium-contrast enhancement [28]. In a series of 64 consecutive patients suspected of GCA, MRI had a sensitivity of 80.6% and a specificity of 97.0%; in these patients in whom MRI was done within the first 10 days of corticosteroid treatment, sensitivity was even higher: 85.7%. In patients with GCA, the mean wall thickness of inflamed artery segments was significantly larger \( (0.74 \pm 0.32 \text{ mm}) \) than in unaffected segments \( (0.39 \pm 0.18 \text{ mm}, P < 0.001) \) and the lumen diameter significantly smaller \( (0.65 \pm 0.38 \text{ mm versus} 0.84 \pm 0.29 \text{ mm}, P < 0.05) \) (figure 3) [29]. Assessment of the cranial involvement, including the frontal and parietal branch of the superficial temporal arteries and the superficial occipital arteries, is feasible with this technique, as well as assessment of intracranial arteries [30]. Aortitis can also be assessed and monitored with MRI and magnetic resonance angiography (MRA), although comparative studies with CT angiography are lacking.

**Figure 3**

Magnetic resonance imaging-image of involved cranial vessels in giant cell arteritis

Note involvement of the left superficial occipital artery, frontal and parietal branch of the left temporal artery and frontal branch of the right temporal artery (arrows). Courtesy of Dr. Thorsten Bley.
Whereas MRI and MRA have a well-defined role in the diagnosis of Takayasu arteritis [31], their place in GCA is less obvious.

Conclusion

A patient with proven vasculitis can be classified as suffering from GCA when at least 3 out of 5 American College of Rheumatology classification criteria for GCA are met [32]. The easiest way to demonstrate vasculitis is by biopsying the temporal artery, but the temporal arteries are not always involved in GCA, and hence biopsy-negative cases of GCA are rather frequent. In these patients, performing FDG-PET scintigraphy is in my opinion the examination of choice to demonstrate vasculitis of the larger arteries. Additionally, it will show in one examination vascular involvement throughout the body. The limited availability and high cost of this technique may be a stumbling block in many countries. To diagnose GCA, there is probably no added value of PET-CT scan compared to PET alone, although an increased aortic wall thickness on CT may point to aortitis in these patients. CT-scan alone is not intended for the diagnosis of GCA, but may show its impact on the aorta. In very experienced hands, ultrasound may replace temporal artery biopsy. MRI can be used occasionally in GCA to demonstrate involvement of a specific arterial branch.

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References


