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ORIGINAL ARTICLE

Giant-cell arteritis: concordance study between aortic CT angiography and FDG-PET/CT in detection of large-vessel involvement

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Abstract
Purpose The purpose of our study was to assess the concordance of aortic CT angiography (CTA) and FDG-PET/CT in the detection of large-vessel involvement at diagnosis in patients with giant-cell arteritis (GCA).
Methods We created a multicenter cohort of patients with GCA diagnosed between 2010 and 2015, and who underwent both FDG-PET/CT and aortic CTA before or in the first ten days following treatment introduction. Eight vascular segments were studied on each procedure. We calculated concordance between both imaging techniques in a per-patient and a per-segment analysis, using Cohen's kappa concordance index.
Results We included 28 patients (21/7 women/men, median age 67 [56–82]). Nineteen patients had large-vessel involvement on PET/CT and 18 of these patients also presented positive findings on CTA. In a per-segment analysis, a median of 5 [1–7] and 3 [1–6] vascular territories were involved on positive PET/CT and CTA, respectively ($p = 0.03$). In qualitative analysis, i.e., positivity of the procedure suggesting a large-vessel involvement, the concordance rate between both procedures was 0.85 [0.64–1]. In quantitative analysis, i.e., per-segment analysis in both procedures, the global concordance rate was 0.64 [0.54–0.75]. Using FDG-PET/CT as a reference, CTA showed excellent sensitivity (95%) and specificity (100%) in a per-patient analysis. In a per-segment analysis, sensitivity and specificity were 61% and 97.9%, respectively.
Conclusions CTA and FDG-PET/CT were both able to detect large-vessel involvement in GCA with comparable results in a per-patient analysis. However, PET/CT showed higher performance in a per-segment analysis, especially in the detection of inflammation of the aorta's branches.

Keywords ^{18}FDG-pet/Ct · CT angiography · Giant-cell arteritis · Large-vessel vasculitis

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Introduction

Giant-cell arteritis (GCA) is the most frequent systemic vasculitis in patients over 50. Cranial vessels, mainly those from the external carotid artery, are affected in most patients, thus explaining the cephalic symptoms [1]. However, it has been shown that the aorta and its main branches are more frequently involved than initially thought, mainly because imaging tools are more widely used at diagnosis and during follow-up [2–6]. Historically, aortic CT angiography (CTA) was the first and most frequently used procedure to demonstrate large-vessel involvement [5, 7]. More recently, other tools, such as ^{18}F–fluorodeoxyglucose (FDG) positron emission tomography (FDG-PET/CT) or aorta magnetic resonance angiography (MRA), have also shown their ability to demonstrate large-vessel vasculitis [2, 3, 6, 8]. Imaging tools are mainly helpful

in the diagnosis of incomplete clinical forms of the disease, especially when temporal artery biopsy (TAB) fails to demonstrate vasculitis [9, 10]. Moreover, large-vessel involvement may be the source of severe complications explaining why routine screening should be mandatory [4, 11, 12]. To date, no recommendations specify which patients should be screened at diagnosis or during follow-up and which imaging procedure should be preferentially used. However, since large sample sized studies demonstrated a high rate of non-symptomatic large-vessel involvement in GCA, some authors recommend controlling large-vessel morphology at diagnosis and during follow-up [13–15]. Aortic CTA can demonstrate changes in the morphology of large vessels, such as wall thickening (circumferential aortic wall thickening ≥2 mm is suggestive of vascular inflammation), vessel stenosis or thrombosis, or aortic dilation or dissection [5, 7, 16]. FDG-PET/CT identifies morphological and metabolic changes in large-vessels, and vascular inflammation can appear as homogeneous and linear vascular FDG uptakes [8]. Over the last few years, the rate of GCA patients undergoing FDG-PET/CT has continually increased. Although aortic CTA and FDG-PET/CT have both shown high sensitivity to detect large-vessel inflammation, no studies have been conducted to analyze the concordance of both tools at GCA diagnosis. Their respective sensitivity and specificity is poorly documented, as the gold-standard procedure remains to be defined in this setting.

In this work, we aimed to assess the concordance of aortic CTA and FDG-PET/CT in the detection of large-vessel involvement in selected GCA patients who underwent both procedures at diagnosis.

Patients and method

Study population

We retrospectively enrolled patients from three French northwestern university hospitals. All patients diagnosed with GCA in these centers are included in a database. Diagnosis was based on the criteria from the American College of Rheumatology [17] and/or the demonstration of large-vessel involvement on imaging and/or a positive biopsy on another site than the temporal artery. For the purpose of this study, we selected patients who performed both FDG-PET/CT and aortic CTA before or in the first ten days following treatment introduction. Reasons to perform both procedures were either to explore atypical presentations (e.g., isolated fever or inflammatory symptoms), for GCA differential diagnosis (e.g., infections or malignancies), or to confirm large-vessel inflammation on a second procedure after the first procedure suggested large-vessel involvement. Patients with one or both procedures performed more than ten days after introduction of glucocorticoids (GC) were not included. Radiologists and nuclear medicine physicians who performed the imaging procedures were aware of the need to analyze large vessels and search for vasculitis, as well as rule out other differential diagnoses such as malignancies or infections.

This study was conducted in compliance with good clinical practices and the Declaration of Helsinki principles. In accordance with French public health law (Art. L 1121–1-1, Art. L 1121–1-2), formal approval from an ethics committee is not required for this type of study. The manuscript was prepared in accordance with STROBE guidelines.

Studied parameters and definitions

Data of enrolled patients included: demographics, cardiovascular risk factors, clinical presentation, lab tests results, temporal artery biopsy (TAB) status, and results of FDG-PET/CT and aortic CTA.

Results of imaging were extracted from the Nuclear Medicine and Radiology reports. In both procedures, eight vascular territories were analyzed, namely thoracic and abdominal aorta, subclavian, carotid, axillary, upper limb, iliofemoral and lower limb arteries. A vascular territory was considered affected on aortic CTA when showing a circumferential and homogeneous thickening ≥2 mm of the vascular wall. Vascular stenoses were also checked. On FDG-PET/CT, all vascular uptakes of equal or superior intensity to that of liver physiologic uptake were considered positive [18]. Circumferential and homogeneous vascular uptakes were suggestive of vasculitis. Focal (non-circumferential) FDG uptake was considered to be an atherosclerotic lesion and thus classified as a negative FDG-PET/CT.

Statistical analyses

Categorical variables are expressed as number (%) and quantitative variables as median [range]. Categorical variables were analyzed with the Chi-square test, and quantitative variables with Wilcoxon's rank-sum test.

Cohen's kappa concordance index was used to analyze concordance between aortic CTA and FDG-PET/CT in a per-patient analysis (i.e., presence or not of a large-vessel involvement) and a per-segment analysis.

The index values are interpreted as: poor ($\kappa < 0$), slight ($\kappa = 0$–0.20), fair ($\kappa = 0.21$–0.40), moderate ($\kappa = 0.41$–0.60), substantial ($\kappa = 0.61$–0.80) and almost perfect ($\kappa = 0.81$–1) concordance.

Using FDG-PET/CT as gold standard, we calculated sensitivity, specificity, accuracy, positive and negative predictive values of aortic CTA in a per-patient and a per-segment analysis.

Table 1 Characteristics of 28 patients with giant-cell arteritis who underwent aortic CT angiography and FDG-PET/CT at diagnosis

Demographics	
Age	67 [56–82]
Women	21 (75)
Cardio-vascular risk factors	
Hypertension	10 (36)
Tobacco use	8 (29)
Dyslipidemia	9 (32)
Diabetes mellitus	5 (18)
Clinical manifestations	
Headaches	14 (50)
Scalp tenderness	6 (21)
Jaw claudication	1 (4)
Ophthalmic troubles	3 (11)
Abnormalities on temporal artery	1 (4)
Polymyalgia rheumatica	11 (39)
Large-vessel claudication	2 (7)
Large-vessel murmur	5 (19)
Isolated constitutional signs	9 (32)
Work-up at diagnosis	
Erythrocyte sedimentation rate, mm	67 [21–141]
C-reactive protein, mg/l	60 [15–390]
Positive temporal artery biopsy	11 (39)
Large-vessel involvement on angio-CT scan	18 (64)
Thoracic aorta	15 (54)
Abdominal aorta	9 (32)
Subclavian arteries	9 (32)
Carotid arteries	7 (25)
Axillary arteries	5 (18)
Upper limb arteries	0 (0)
Ilio-femoral arteries	5 (18)
Lower limb arteries	2 (7)
Large-vessel involvement on FDG-PET/CT	19 (68)
Thoracic aorta	19 (68)
Abdominal aorta	12 (43)
Subclavian arteries	16 (57)
Carotid arteries	12 (43)
Axillary arteries	11 (39)
Upper limb arteries	0
Ilio-femoral arteries	9 (32)
Lower limb arteries	1 (4)

Unless indicated otherwise, values are displayed as an absolute number, (%) or median [range]

CTA: computed tomography angiography; FDG-PET/CT: ^{18}F–fluorodeoxyglucose positron emission tomography

Statistical analyses were computed with JMP v9.0.1 (2010 SAS Institute Inc.), with $P < 0.05$ defining statistical significance.

Table 2 Concordance between FDG-PET/CT and CT angiography in the diagnosis of large-vessel involvement in giant-cell arteritis

	κ [95% CI]
Aorta and its main branches	0.64 [0.54–0.75]
Thoracic aorta	0.71 [0.45–0.96]
Abdominal aorta	0.62 [0.33–0.91]
Subclavian arteries	0.52 [0.26–0.79]
Carotid arteries	0.62 [0.33–0.90]
Axillary arteries	0.50 [0.20–0.81]
Upper limb arteries	–
Ilio-femoral arteries	0.63 [0.32–0.94]
Lower limb arteries	–

FDG-PET/CT: ^{18}F–fluorodeoxyglucose positron emission tomography; CT: computed tomography

Results

Fifty-eight patients were assessed, but 30 were excluded because one of the two procedures was performed more than 10 days after GC introduction. Finally, our study included 28 patients (21/7 women/men, median age 67 [56–82], details in Table 1) who underwent both procedures before or in the first ten days following treatment introduction. GCA diagnosis was done in all patients between 2010 and 2015. Median number of ACR criteria was three [2–4] and 14 (50%) patients did not suffer from headaches. Twenty-five patients underwent both aortic CTA and PET/CT before any treatment, and three had aortic CTA before GC but performed PET/CT 8–10 days after treatment onset.

In 23 (82%) patients, CTA was performed first and was positive in 15 patients. PET/CT was performed in the following (median: 8 [2–17]) days and was positive in these 15 patients and in another additional one. In the five other patients, PET/CT was performed first and was followed by CTA, 10 [3–15] days later. Three out of these five PET/CT were positive, and CTA was also positive in these patients. Altogether, PET/CT was positive in 19 patients, among which 18 also had a positive CTA. The patient with positive PET/CT but negative CTA had thoracic aorta as well as subclavian, carotid and axillary artery involvement. This was the only patient of the study with non-concordant results, i.e., with CTA failing to identify large vessel involvement observed on PET/CT. The nine patients with negative CTA also had negative PET/CT. Thereby, no patient had positive CTA and negative PET/CT. Among the three patients who performed PET/CT after treatment onset, two had both negative CTA and PET/CT, and the last had both positive procedures. Only one patient presented stenotic lesions on subclavian arteries on CTA, which were also enhanced by FDG on PET/CT.

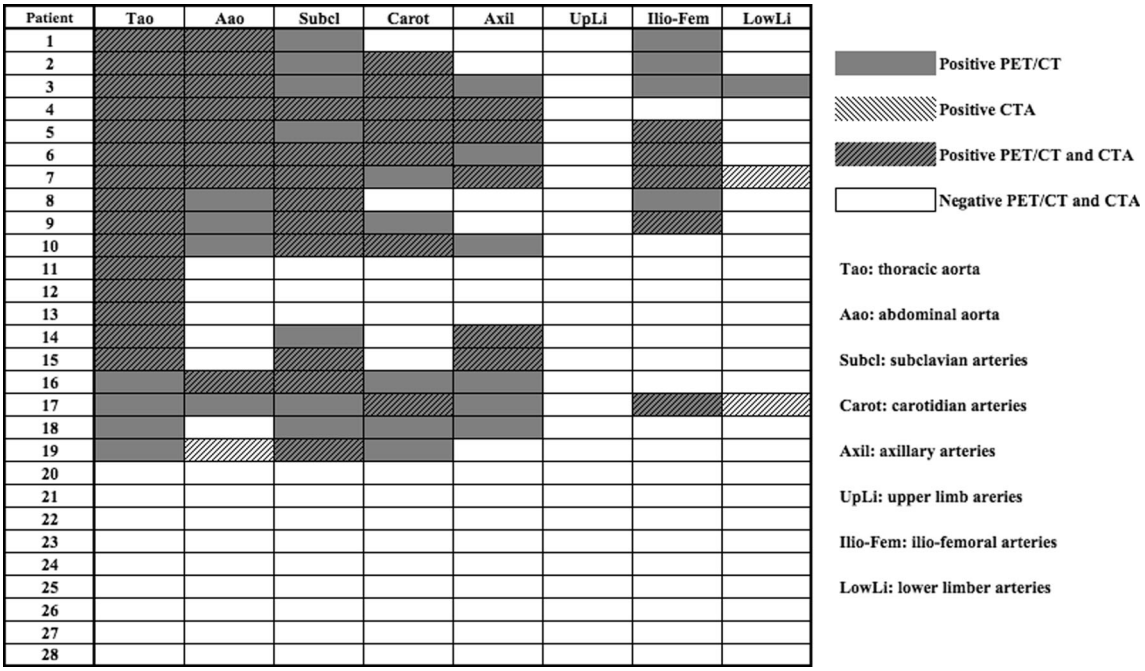

Fig. 1 Results of both aortic CT angiography and ^{18}F–fluorodeoxyglucose positron emission tomography in 28 patients with giant-cell arteritis screened for large-vessel involvement

In a per-segment analysis, a median of 5 [1–7] and 3 [1–6] vascular territories were involved on positive PET/CT and CTA, respectively ($p = 0.03$).

In qualitative analysis, i.e., positivity of the procedure suggesting large-vessel involvement, the concordance rate between both procedures was 0.85 [0.64–1]. In quantitative analysis, i.e., per-segment analysis in both procedures, the global concordance rate was 0.64 [0.54–0.75] (Table 2). Among the 224 vascular territories analyzed on both procedures in the 28 patients, 80 were enhanced on FDG-PET/CT and 49 (61%) of them were also involved on CTA (Fig. 1). Thirty-one (14%) vascular territories were only enhanced on PET/CT and, conversely, three vascular territories were involved on CTA, but not on FDG-PET/CT.

Detailed concordances between both procedures for each vascular segment are shown in Table 2. A better concordance between both procedures was observed for larger vessels (namely thoracic and abdominal aorta as well as carotid and ilio-femoral arteries, with κ coefficient ranging between 0.62 and 0.71). In smaller vessels' assessment, concordance between both imaging tools decreased.

Finally, considering FDG-PET/CT as the standard procedure, sensitivity, specificity, accuracy, positive and negative predictive values of CTA are indicated in Table 3, in a per-patient and in a per-segment analysis. In large-vessel involvement assessment, CTA showed excellent sensitivity (95%) and specificity (100%) in per-patient analysis. However, in per-segment analysis, sensitivity was low (61%), whereas specificity remained high (97.9%).

Discussion

Aortic CTA and FDG-PET/CT have both shown their ability to detect large-vessel involvement in GCA, but limited data exist on the comparison of the two imaging tools in this setting. Herein, we showed that both procedures were comparatively able to detect GCA large-vessel involvement in patients screened at diagnosis. CTA showed excellent concordance with FDG-PET/CT in a qualitative analysis. Indeed, both procedures were able to determine in a per-patient analysis which patient had large-vessel involvement, with excellent specificity and

Table 3 Diagnostic performance of aortic CT angiography in 28 patients with giant-cell arteritis, compared to FDG-PET/CT

	Sensitivity	Specificity	Accuracy	PPV	NPV
Diagnosis per patient	95% (18/19)	100% (9/9)	96.4% (27/28)	100 [82.4–100]	90 [59.6–98.2]
Diagnosis per segment	61% (49/80)	97.9% (141/144)	84.8% (190/224)	94.2 [84.4–98]	82 [75.6–87]

FDG-PET/CT: ^{18}F–fluorodeoxyglucose positron emission tomography; PPV: positive predictive value; NPV: negative predictive value

sensitivity of 100% and 95% for CTA, respectively, in comparison to FDG-PET/CT. The latter procedure was used as a reference because of its slightly better sensitivity in per-patient analysis and the significantly higher number of vascular territories involved in per-segment analysis in comparison to CTA.

It appears relevant to assess large-vessel involvement at GCA diagnosis and during follow-up. First, large-vessel involvement in GCA is often non-symptomatic [5, 10, 19]. Second, in patients with atypical presentation (e.g., without cranial symptoms or with isolated constitutionals signs) or with negative TAB, demonstration of large-vessel involvement on imaging tools is very helpful in the working diagnosis of GCA. Finally, it has been shown that patients with large-vessel involvement may present more aortic complications and may be more prone to die from cardiovascular disease [4, 11, 12].

Our results, in addition to the practical and economic considerations regarding the easier access and less expensive cost of CTA, suggest it should be the first choice of imaging to detect large-vessel involvement, since its sensitivity remains high and comparable to that of FDG PET/CT. PET/CT may be used secondly, especially in patients with CTA contraindications (e.g., renal insufficiency). However, in the context of isolated constitutional symptoms or persistent isolated biologic inflammatory syndrome, PET/CT may be preferred and may be a more sensitive tool to diagnose GCA and/or differential diagnoses such as malignancies or infection. Our study also indicated that PET/CT detected additional involved segments and showed a more precise and exhaustive cartography of involved territories. Concordance between both procedures was good for thoracic aorta, but decreased for smaller vessels (remaining >0.5 in all vascular territories) for which PET/CT showed higher performance than CTA. Further studies are required to determine the best imaging strategy to screen large-vessels inflammation under treatment and to detect aortic complications during follow-up.

Our results are concordant with the few published data in the literature. In the study from Larivière et al., 15 GCA patients and nine controls underwent both procedures at diagnosis. In a per-patient analysis, PET/CT and CTA led to the same conclusions in 19/24 patients. In a per-segment analysis, as in our study, PET/CT showed higher performance than CTA [20]. In the study from Daumas et al., 20 patients underwent both procedures. However, this study lacked information about the procedures' timing relative to GC introduction. Concordance between both procedures for the analysis of the thoracic aorta ranged between 0.63 and 0.88 and decreased when assessing the abdominal aorta and the main aortic branches, with PET/CT detecting more involved territories than CTA. All patients with negative CTA also had negative PET/CT [21].

Besides PET/CT and CTA, other imaging tools may be used to assess large-vessel involvement, such as magnetic resonance imaging (MRI) or Doppler ultrasound. However, the importance of these procedures in the working diagnosis of GCA is unknown, and comparative studies between different imaging tools are lacking. Comparisons between PET/CT and MRI have been conducted in a few small-sized studies with controversial results [8, 22, 23]. Other studies comparing color-coded Doppler sonography or contrast-enhanced ultrasound to PET/CT showed a good concordance in the assessment of large vessels, such as subclavian, axillary or carotid arteries [3, 24–26].

In addition to the strengths of our study, we acknowledge some limitations. First of all, the retrospective design may have limited the exhaustiveness of retrieved information, especially regarding the results of imaging tools. The absence of a central review of each imaging may have led to an underestimation of lesions on CTA. However, radiologists who performed CTA were specifically asked to analyze large vessels and were aware of the suspicion of large-vessel vasculitis. Moreover, the rates of involvement of different vascular territories in our CTA results were not very different from those described in other works [5, 16]. Secondly, the small sample of our study may limit the interpretation of our results. Finally, as our series is multicenter, different devices from various manufacturers may have been used with different protocols. However, this limitation is balanced out by the excellent concordance of positivity/negativity between CTA and PET/CT in the three centers.

In conclusion, our study showed that CTA and FDG-PET/CT were both able to detect large-vessel involvement in GCA with comparable sensitivity and specificity in a per-patient analysis. PET/CT may however be more sensitive than CTA in the detection of inflammation of the aorta's branches with a better per-segment diagnostic performance. Our study thus suggests that CTA should be the first-intention procedure to detect large-vessel involvement given its lower cost and easier access. Further prospective studies are expected to confirm these data and to determine the place of each imaging technique, including others such as MRA or Doppler ultrasonography.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no competing interests.

Ethical approval This study was in accordance with the ethical standards of the institutional research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

Informed consent In accordance with French public health law (Art. L 1121–1-1, Art. L 1121–1-2), formal informed consent is not required for this type of study (retrospective observational study).

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