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Association between vascular FDG uptake at diagnosis and evolution in aortic dimensions in giant cell arteritis: a prospective study

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Abstract

Background: Retrospective studies have shown that giant cell arteritis (GCA) patients with vascular 18F-fluorodeoxyglucose (FDG) uptake at diagnosis are at increased risk of developing aortic complications.

Objective: To evaluate the association between vascular FDG uptake at diagnosis and the evolution of aortic dimensions in GCA patients.

Design: Prospective cohort study

Setting: University Hospitals Leuven, 2012-2020

Patients: 100 GCA patients with FDG PET imaging at diagnosis ≤3 days after initiation of glucocorticoids and followed for ≥2 years.

Measurements: PET scans were scored (0-3) at 7 vascular areas and a total vascular score (TVS) was calculated. PET scans were considered positive in case of FDG uptake ≥ grade 2 in any large vessel. Patients underwent CT imaging at diagnosis and yearly thereafter for a maximum of 10 years. The association between vascular FDG uptake and aortic dimensions was estimated by linear mixed effect models with random intercept and slope.

Results: The increase in ascending and descending aortic diameter and in thoracic aortic volume was higher in patients with a positive PET scan compared to those without (p=0.009, p=0.01, and p=0.008, respectively). This increase was also significantly associated with TVS (p=0.007, p=0.03, and p=0.003, respectively). FDG uptake was not associated with an increase in abdominal aortic dimensions. Thoracic aortic aneurysms were more frequently observed in patients with a positive PET scan (aOR 7.19, 95%-CI 1.55-54.18, p=0.02).

Limitations: The lengthy inclusion and follow-up period resulted in the use of different PET machines and missing data.

Conclusion: Higher TVS was associated with greater yearly increase in thoracic aortic dimensions. Performing PET imaging at diagnosis may help to estimate the risk of aortic aneurysm formation.

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Introduction

Giant cell arteritis (GCA) is a large vessel vasculitis that preferentially affects the cranial arteries, the aorta, and its proximal branches (1). The prevalence of GCA increases with age and is estimated at 125-250 per 100 000 in people over 50 years old in northern Europe and North America (2).

For the diagnosis of GCA, the European Alliance of Associations for Rheumatology (EULAR) recommends early imaging (3). Ultrasound is recommended for the assessment of GCA with cranial artery involvement with magnetic resonance imaging (MRI) as an alternative (3). Our group has introduced ^{18}F-fluorodeoxyglucose (FDG) positron emission tomography (PET)-scintigraphy in the assessment of large vessel vasculitis (4,5). PET/computed tomography (CT) and MRI are currently recommended for the assessment of large vessel involvement with similar diagnostic accuracy (6).

Two severe complications of GCA are sudden irreversible vision loss and aortic aneurysm formation and dissection. Vision loss most frequently occurs before or within the first days of initiation of treatment with glucocorticoids (7). In contrast, aortic aneurysm may be present at diagnosis, but typically occurs during follow-up. However, the exact timing of aortic aneurysm formation in GCA patients remains unclear.

Patients with GCA have a 3 to 17-fold increased risk of developing thoracic aortic aneurysms (8–11). A meta-analysis of studies with systematic imaging reported a pooled prevalence of thoracic aortic aneurysm of 15% (12). GCA patients have no or only a slightly increased risk of abdominal aortic aneurysms (8–11). Predictors for thoracic aneurysms were reported with inconsistent results (12). However, four retrospective studies have indicated that FDG uptake in large vessels at diagnosis increases the risk of developing aortic complications during follow-up (13–16). Prospective studies confirming these findings are lacking. The aim of this study was to evaluate the association between FDG uptake in large vessels at diagnosis and the evolution of aortic dimensions in a prospective cohort of GCA patients.

Methods

Patient population

We prospectively included patients with GCA, who were evaluated by the Department of General Internal Medicine of the University Hospitals Leuven between 2012 and 2020 and who had undergone FDG PET imaging at diagnosis within 3 days after initiation of glucocorticoids. Patients with a previous diagnosis of GCA, in whom a PET scan and yearly CT of the aorta were available, were also included. Patients who were followed for less than two years were excluded.

The study was conducted in accordance with the Declaration of Helsinki and approved by the ethical committee of the University Hospitals Leuven. All patients gave informed consent. The study was registered in advance in ClinicalTrials.gov (NCT01588483).

Data collection

We collected the following patient data from the electronic health record: age, sex, date of diagnosis, duration of symptoms until diagnosis, symptoms at diagnosis, cardiovascular risk factors and medication, erythrocyte sedimentation rate (ESR; mm/h), C-reactive protein (CRP; mg/l), temporal artery biopsy (TAB) result, duration of follow-up, total duration (in weeks) and

cumulative dose in the first two years of glucocorticoid treatment, use of glucocorticoid-sparing agents, relapses, aortic complications (dilatation or dissection and region), vascular stenosis, vascular surgery, myocardial infarction, cerebrovascular accident (CVA), anterior ischemic optic neuropathy (AION), and mortality during follow-up.

Definitions

The diagnosis of GCA was based on the judgement of two experienced clinicians (DB and SV), considering all available information (clinical data, biochemical, radiological, PET and TAB results, and evolution during follow-up). Relapse was defined as recurrence of clinical symptoms compatible with GCA or polymyalgia rheumatica (PMR) and/or increase of inflammatory markers requiring escalation of treatment. We created a cardiovascular risk score by adding the following cardiovascular risk factors with a maximum of 10 points: history of myocardial infarction or angor, peripheral vascular disease, and stroke were assigned 2 points; diabetes, smoking, use of statins, and use of antihypertensive medication were assigned 1 point.

PET imaging and analysis

Patients were required to fast for at least 6 hours before intravenous injection of 4-5 MBq/kg of FDG, and glycemia levels were determined in all patients (as per procedure, to be < 140 mg/dl). A whole-body PET scan was performed 60 min after tracer administration. PET scans were performed between 2003 and 2020, acquired on a ECAT HR + PET camera, Hirez Biograph 16 PET/CT, Truepoint Biograph 40 PET/CT (Siemens, Knoxville, TN, USA) or GE Discovery MI 4-ring PET/CT system (GE, Milwaukee, WI, USA). Because of scan duration, HR+ data were not corrected for attenuation using transmission scanning. On the PET/CT systems, either a low-dose non-diagnostic CT scan or a diagnostic CT scan was performed immediately before PET acquisition. Non-attenuation corrected PET images were available for all included patients and attenuation-corrected PET images were only available for the patients who were scanned with a PET/CT system (n=63). PET data were corrected for scatter and randoms. Data were reconstructed using iterative OSEM reconstruction, with parameters optimized over the years (FWHM HR+ 6-7 mm, for the Truepoint 5 mm).

Reconstructed PET images were re-evaluated visually by a specialist in nuclear medicine (LB), who was blinded for all other patient information. FDG PET uptake was scored semi-quantitatively at 7 vascular regions (thoracic and abdominal aorta, subclavian, axillary, carotid, iliac, and femoral arteries) as 0 (no FDG uptake), 1 (minimal but not negligible FDG uptake), 2 (clearly increased FDG uptake), or 3 (very marked FDG uptake). PET scans were considered positive in case of FDG uptake ≥ grade 2 in any large vessel. Additionally, a total vascular score (TVS) was calculated ranging from 0 (no vascular FDG uptake in any of the 7 vascular regions) to 21 (vascular FDG uptake scored 3 in all 7 segments) (17). Subclavian, axillary, carotid, iliac, and femoral arteries were counted as 1 vascular region each: when the score differed from right to left artery, the highest score was taken for that vascular region. The intensity of FDG uptake in affected vessels was measured by dividing TVS by the number of vessels with FDG uptake ≥ grade 2. In addition, to assess cranial vasculitis, the vertebral, maxillary, occipital and temporal arteries were scored similarly.

CT imaging and analysis

Patients underwent a CT scan of the thorax and abdomen at diagnosis and yearly thereafter for a maximum of 10 years. CT scans were preferentially performed without intravenous

contrast. A contrast-enhanced CT scan or PET/CT scan was used if a non-enhanced CT scan was not available. The aortic diameter was measured perpendicular to the axis of blood flow at six different levels (ascending aorta, aortic arch, descending thoracic aorta, suprarenal, juxtarenal and infrarenal aorta) and the thoracic and abdominal aortic volumes were measured. To obtain the volume, the thoracic and abdominal aorta were segmented semi-automatically using MMWP Volume software (Siemens, Erlangen, Germany). Next, the volumes of both parts were calculated automatically. To avoid interobserver variability, the measurements were performed by the same author (diameters by LM and volumes by WC). Both were unaware of the PET findings. The ascending aorta, aortic arch, descending aorta, and abdominal aorta were considered aneurysmatic when the diameter was ≥45, ≥40, ≥35 and ≥30 mm respectively (14,15).

Statistical analysis

Categorical and continuous variables were expressed as count and percentage and as mean and standard deviation or median and interquartile range (IQR) as appropriate. Chi square tests, Fisher's exact test, unpaired t-test, or Mann-Whitney U tests were used to compare characteristics between patients with a positive and negative PET scan and between patients with and without thoracic aortic aneurysm as appropriate. The associations between a positive PET scan and aortic diameters and volumes were estimated by linear mixed effect models with random intercept and slope in time with and without adjustment for age, sex, cardiovascular risk score, CT or PET/CT scan, and intravenous contrast. These confounding factors were chosen for biological and technical reasons. Subgroup analyses comparing patients with a positive and negative PET scan in the thoracic and abdominal aorta were performed. In addition, the association between TVS, the number of vessels with FDG uptake ≥ grade 2 and the intensity of FDG uptake in affected vessels on the one hand and evolution of the aortic diameters and volumes on the other hand were assessed. Logistic regression models were fitted to analyze the association between a positive PET scan and thoracic aortic aneurysm with and without adjustment for the same variables. All statistical tests were two-tailed with significance set at the $p<0.05$ level. Statistical analysis was performed in R Studio (version 2022.06.23, The R Foundation for Statistical Computing) with inclusion of the *lme4, sjPlot,* and *ggplot2* packages.

Role of the funding source

This study received no funding.

Results

136 GCA patients underwent a PET scan between 2003 and 2020 and signed informed consent. Twenty patients were excluded because they received treatment with glucocorticoids for more than three days prior to PET imaging. Sixteen patients were followed less than two years. Finally, 100 patients (mean age 70 years, 68% females) were included, of whom 74 (74%) patients had FDG uptake ≥ grade 2 in any large vessel, 60 (60%) in the thoracic aorta, and 49 (49%) in the abdominal aorta. In these patients, 603 CT scans were performed, of which 507 (84%) non-enhanced CT scans, 14 (2%) contrast-enhanced CT scans and 82 (14%) PET/CT scans. Median follow-up was 80 months (IQR 47-110). Fifteen (15%) patients received glucocorticoids for less than three days prior to PET imaging; 85 (85%) were steroid-naive. Median TVS was 14 (IQR 6-16, range 2-21) in the PET positive group and 0 (IQR 0-1, range 0-3) in the PET negative group. FDG uptake ≥ grade 2 was most frequently observed in the subclavian arteries (64%), followed by ascending aorta (59%), aortic arch (57%),

descending aorta (57%), abdominal aorta (49%), carotid arteries (48%), axillary arteries (48%), iliac arteries (22%), and femoral arteries (20%). Forty eight percent of patients had increased FDG uptake in the cranial arteries, all of whom had FDG uptake in the vertebral arteries. The maxillary, temporal, and occipital arteries were affected in 36%, 15%, and 11% respectively.

The baseline characteristics are presented in Table 1. Patients with a positive PET scan were younger (68 versus 74 years, p=0.001) and more frequently female (77% versus 42%, p=0.001) compared to those with a negative PET scan. The symptom duration until diagnosis was significantly longer in patients with a positive PET scan (8 versus 3 weeks, p<0.001). Patients without vascular FDG uptake more frequently had cranial symptoms (96% versus 69%, p=0.006) and tended to have more PMR (54% versus 34%, p=0.07), whereas those with vascular FDG uptake more often had constitutional symptoms (95% versus 65%, p<0.001). There were no significant differences in cardiovascular risk factors, proportion of patients with a positive temporal artery biopsy, or inflammatory markers between the PET positive and PET negative group.

The increase in ascending and descending aortic diameter and in thoracic aortic volume was higher in patients with a positive PET scan compared to those without (p=0.009, p=0.01 and p=0.008, respectively) (Table 2 and Supplementary Tables 1 and 2). In patients with a positive PET scan in the thoracic aorta, the increase was only significantly higher in the ascending aortic diameter and in thoracic aortic volume (both p=0.005) (Table 2 and Supplementary Tables 3 and 4). However, there was also a trend to a greater increase in the diameter of the descending aorta and aortic arch (p=0.06 and p=0.07, respectively). Vascular FDG uptake was not associated with an increase in abdominal aortic diameters nor volume (Table 2 and Supplementary Tables 5 and 6). The thoracic aortic diameters and volume were positively associated with TVS (Table 3, Figure 1 and Supplementary Tables 7 and 8). There was no significant association between the abdominal aortic diameters and volume on the one hand and TVS on the other hand. The ascending and descending aortic diameter and thoracic aortic volume were also positively associated with the number of vessels with FDG uptake ≥ grade 2 and with the intensity of FDG uptake in affected vessels (Supplementary Tables 9-12). As expected, TVS, the number of affected vessels, and the intensity of FDG uptake in affected vessels are correlated with each other, with the strongest correlation between TVS and the number of affected vessels (Supplementary Table 13).

Twenty-one patients developed an aortic aneurysm, which was already present on the first CT scan in six patients. The median time since diagnosis to develop an aortic aneurysm was 37 months (IQR 19-60) for any aneurysm and 40 months (IQR 18-61) for thoracic aortic aneurysm. Eighteen patients had an aneurysm in the descending aorta, five in the ascending aorta, five in the aortic arch, and four in the abdominal aorta. In three of the four patients with an abdominal aortic aneurysm, the aneurysm was located in the suprarenal aorta and these patients also had a thoracic aortic aneurysm. The patient with an isolated abdominal aortic aneurysm had an infrarenal aneurysm. Logistic regression analysis revealed that thoracic aortic aneurysms occurred more frequently in patients with a positive PET scan (24% versus 8%, aOR 7.19, 95%-CI 1.55-54.18, p=0.02) and in patients with a positive PET scan in the thoracic aorta (27% versus 10%, aOR 6.06, 95%-CI 1.68-27.62, p=0.01) (Supplementary Tables 14 and 15). Aortic aneurysm occurred in 16 of the 18 (89%) PET positive patients in a region with FDG uptake at diagnosis. Two patients with high TVS (15 and 16, maximum 21) needed elective surgery for ascending aortic aneurysm. Histopathological examination showed

degenerative changes, cystic media necrosis and mild lymphocytic inflammation in the adventitia in both patients and also in the media in one patient.

As an exploratory analysis, we examined differences between patients with and without thoracic aneurysms (Table 4). Patients who developed a thoracic aneurysm, tended to have higher TVS (14 versus 6, p=0.05) with both higher number of affected vessels (5 versus 2, p=0.03), and higher intensity of FDG uptake in affected vessels (2.8 versus 2.7, p=0.04). They also had a longer symptom duration until diagnosis (8 versus 6 weeks, p=0.04), and higher inflammatory markers at diagnosis (CRP 121 versus 78 mg/l, p=0.02 and ESR 98 versus 67 mm/h, p=0.04). There were no significant differences in age, sex, cardiovascular risk factors, symptoms at diagnosis, temporal artery biopsy results, duration of glucocorticoids, cumulative dose of glucocorticoids in the first two years, use of glucocorticoid-sparing agents, relapse rate, cardiovascular events during follow-up, or mortality.

Discussion

In this prospective study, we found that GCA patients with a positive PET scan had a greater increase in ascending and descending aortic diameter and thoracic aortic volume compared to those with a negative scan. There were no differences in abdominal aortic diameters and volume. In addition, higher TVS was associated with greater yearly increase in thoracic aortic diameters and volume. In patients without elevated vascular FDG uptake, the increase in aortic diameters seems to be similar to the general population with a reported yearly increase of about 0.1-0.2 mm (18). Vascular and more specifically thoracic aortic FDG uptake at diagnosis was an independent risk factor for developing thoracic aortic aneurysms.

These findings are consistent with earlier retrospective studies (13–16). Our group first showed that patients with aortic FDG uptake at diagnosis had a significantly larger ascending and descending aortic diameter and thoracic aortic volume during follow-up (13). In a multicenter study of de Boysson et al. 9% of patients developed aortic dilatation, all of whom had FDG uptake in large vessels at diagnosis or during follow-up (14). Afterwards, they confirmed that large vessel inflammation is a predictor of aortic dilatation in a larger, multicenter, retrospective cohort (15). Muratore et al. reported significantly larger thoracic and abdominal diameters in patients with FDG uptake grade 3 compared to those with FDG uptake ≤ grade 2 (16).

The mechanism of aneurysm formation in GCA patients remains unclear. It is sometimes hypothesized that persistent subclinical vasculitis activity leads to cumulative damage to the aortic wall (12,19). However, histopathological examination of the aorta after surgery mostly revealed extensive disruption of elastic fibers in the media with only mild and scattered inflammation in the media and/or adventitia (20–22), which we also found in two patients who required elective surgery for an ascending aortic aneurysm in our cohort. In 89% of PET positive patients aortic dilatation occurred in a vascular region with elevated FDG uptake at diagnosis. In addition, we found a dose-response relation with a positive association between TVS and thoracic aortic diameters and volume. Both the number of vessels with FDG uptake ≥ grade 2 and the intensity of FDG uptake in affected vessels were associated with the evolution in the ascending and descending aortic diameter and thoracic aortic volume. However, the extent and the intensity of vessel involvement were correlated, which we assume to be related to patients with severe large vessel vasculitis having both larger extent of affected vessels and a higher intensity of inflammation in the affected vessels. Moreover, patients who developed a thoracic aneurysm, had a longer symptom duration until diagnosis and had higher

inflammatory markers at diagnosis. Inflammatory markers were also higher in patients with aortic aneurysms in the study of Gonzalez-Gay et al. (23), but this was not significant in several other studies (13,14,16,19,24,25). Blockmans et al. and Nuenninghoff et al. also found a longer symptom duration until diagnosis in patients with aortic dilatation (13,26), but this was not confirmed in two other studies (19,23). There were no significant differences in cardiovascular risk factors in patients with and without thoracic aneurysms. Our findings suggest that the intensity, duration and extent of initial inflammation rather than the persistence of inflammatory activity determines the risk of subsequent aortic dilatation. This intense inflammation probably weakens the aortic wall, which then undergoes progressive dilatation due to deficient vascular remodeling and mechanical forces.

There is no consensus on the screening for the development of aortic aneurysms in GCA patients. EULAR and American College of Rheumatology (ACR) guidelines currently do not recommend routinely screening for aortic dilatation (3,27,28). In contrast, the American Heart Association (AHA)/American College of Cardiology (ACC) Joint Committee recommends annual surveillance imaging with CT, MRI, or PET/CT (29). This study confirms that vascular FDG uptake is an independent predictor of thoracic aortic aneurysms with a higher increase in thoracic aortic diameters and volume in patients with higher TVS. One fourth of patients with a positive PET scan developed a thoracic aortic aneurysm. These aneurysms most frequently occurred in the descending aorta in a median time since diagnosis of 40 months, but the two patients who needed surgery, had an ascending aortic aneurysm. Follow-up of aortic dimensions seems to be warranted in GCA patients, especially in those with high intensity and broad extent of vascular inflammation. However, the added value of screening and the interval required should be addressed in future studies.

Consistent with previous studies (15,30,31), we found that patients with a positive PET scan were younger, were more frequently female, and had a longer symptom duration until diagnosis. Patients with vascular FDG uptake more often had constitutional symptoms, whereas cranial symptoms and PMR more frequently occurred in those without vascular FDG uptake. However, these symptoms are not specific enough to differentiate patients with and without large vessel vasculitis clinically. Thus, to estimate the future risk of aortic aneurysm formation, performing PET imaging at diagnosis before or shortly after the start of glucocorticoid treatment in GCA patients would be advisable.

Strengths of this study include that it is the first prospective study which addresses the impact of vascular FDG uptake on the evolution of aortic dimensions. In addition, a large cohort of GCA patients was followed for a long time in this study. Our study also has several limitations. First, due to the long inclusion period PET scans were performed on different PET systems with increasing device quality over time. In addition, CT scans were preferentially performed without intravenous contrast, but a contrast-enhanced CT scan or a PET/CT scan was used if a non-enhanced CT scan was not available. However, we corrected for this in the linear mixed model and logistic regression analyses. Third, due to the long follow-up a substantial number of CT scans were missing. Fourth, this was a single-center study, which probably limits the generalizability. Finally, the treatment was at the discretion of the physician, so we cannot exclude an effect of differences in treatment on the evolution of aortic dimensions. However, the duration of glucocorticoid treatment, the cumulative glucocorticoid dose in the first two years and the use of glucocorticoid-sparing agents were not significantly different in patients with and without thoracic aneurysms.

In conclusion, higher TVS was associated with greater yearly increase in thoracic aortic diameters and volume. Vascular FDG uptake was not associated with an increase in abdominal aortic diameters nor volume. Vascular and more specifically thoracic aortic FDG uptake at diagnosis is an independent risk factor for developing thoracic aortic aneurysms in GCA patients. In addition to diagnostic information, performing PET imaging at diagnosis in GCA patients would help to estimate the future risk of aortic aneurysm formation. Follow-up of aortic dimensions may be warranted in patients with thoracic aortic FDG uptake or a high TVS.

Conflict of Interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Author Contributions

LM: Conceptualization, Methodology, Validation, Investigation, Formal analysis, Writing – Original Draft, Writing – Review & Editing, Visualization; WC: Conceptualization, Methodology, Validation, Investigation, Writing – Review & Editing; LB: Methodology, Validation, Investigation, Writing – Review & Editing; AB: Conceptualization, Methodology, Writing – Review & Editing; GM: Methodology, Formal analysis, Writing – Review & Editing; SV: Investigation, Writing – Review & Editing, Supervision; KVL: Writing – Review & Editing, supervision; EC: Investigation, Writing – Review & Editing, DB: Conceptualization, Methodology, Investigation, Writing – Review & Editing, Supervision

References

1. Jennette JC, Falk RJ, Bacon PA, Basu N, Cid MC, Ferrario F, et al. 2012 Revised International Chapel Hill consensus conference nomenclature of vasculitides. Arthritis Rheum. 2013;65(1):1–11.
2. Watts RA, Hatemi G, Burns JC, Mohammad AJ. Global epidemiology of vasculitis. Nat Rev Rheumatol. 2022;18(1):22–34.
3. Dejaco C, Ramiro S, Duftner C, Besson FL, Bley TA, Blockmans D, et al. EULAR recommendations for the use of imaging in large vessel vasculitis in clinical practice. Ann Rheum Dis. 2018;77(5):636–43.
4. Blockmans D, Maes A, Stroobants S, Nuyts J, Bormans G, Knockaert D, et al. New arguments for a vasculitic nature of polymyalgia rheumatica using positron emission tomography. Rheumatology. 1999;38(5):444–7.
5. Blockmans D, Stroobants S, Maes A, Mortelmans L. Positron Emission Tomography in Giant Cell Arteritis and Polymyalgia Rheumatica : Evidence for Inflammation of the Aortic Arch. Am J Med. 2000;108(3):246–9.
6. Hellmich B, Agueda A, Monti S, Buttgereit F, De Boysson H, Brouwer E, et al. 2018 Update of the EULAR recommendations for the management of large vessel vasculitis. Ann Rheum Dis. 2020;79(1):19–130.
7. Soriano A, Muratore F, Pipitone N, Boiardi L, Cimino L, Salvarani C. Visual loss and other cranial ischaemic complications in giant cell arteritis. Nat Rev Rheumatol. 2017 Aug;13(8):476–84.
8. Evans JM, O'Fallon WM, Hunder GG. Increased incidence of aortic aneurysm and dissection in giant cell (temporal) arteritis: A population-based study. Ann Intern Med. 1995;122(7):502–7.
9. Robson JC, Kiran A, Maskell J, Hutchings A, Arden N, Dasgupta B, et al. The relative risk of aortic aneurysm in patients with giant cell arteritis compared with the general population of the UK. Ann Rheum Dis. 2015;74(1):129–35.
10. Molloy ES, Kirchner H, Murray P. Cardiovascular outcomes and in-hospital mortality in

giant cell arteritis. APMIS. 2009;117(Suppl s127):83–4.
11. Therkildsen P, De Thurah A, Nielsen BD, Hansen IT, Eldrup N, Nørgaard M, et al. Increased risk of thoracic aortic complications among patients with giant cell arteritis: A nationwide, population-based cohort study. Rheumatol. 2022;61(7):2931–41.
12. Mackie SL, Hensor EMA, Morgan AW, Pease CT. Should i send my patient with previous giant cell arteritis for imaging of the thoracic aorta? A systematic literature review and meta-analysis. Ann Rheum Dis. 2014;73(1):143–8.
13. Blockmans D, Coudyzer W, Vanderschueren S, Stroobants S, Loeckx D, Heye S, et al. Relationship between fluorodeoxyglucose uptake in the large vessels and late aortic diameter in giant cell arteritis. Rheumatology. 2008;47(8):1179–84.
14. De Boysson H, Liozon E, Lambert M, Parienti JJ, Artigues N, Geffray L, et al. 18 F-fluorodeoxyglucose positron emission tomography and the risk of subsequent aortic complications in giant-cell arteritis. Medicine (Baltimore). 2016;95(26).
15. de Boysson H, Daumas A, Vautier M, Parienti J-J, Liozon E, Lambert M, et al. Large-vessel involvement and aortic dilation in giant-cell arteritis. A multicenter study of 549 patients. Autoimmun Rev. 2018 Apr;17(4):391–8.
16. Muratore F, Crescentini F, Spaggiari L, Pazzola G, Casali M, Boiardi L, et al. Aortic dilatation in patients with large vessel vasculitis: A longitudinal case control study using PET/CT. Semin Arthritis Rheum. 2019;48(6):1074–82.
17. Blockmans D, Ceuninck L de, Vanderschueren S, Knockaert D, Mortelmans L, Bobbaers H. Repetitive 18F-fluorodeoxyglucose positron emission tomography in giant cell arteritis: a prospective study of 35 patients. Arthritis Care Res (Hoboken). 2006;55(1):131–7.
18. Rogers IS, Massaro JM, Truong QA, Mahabadi AA, Kriegel MF, Fox CS, et al. Distribution, Determinants, and Normal Reference values of Thoracic and Abdominal Aortic Diameters by Computed Tomography (From the Framingham Heart Study). Am J Cardiol. 2013;111(10):1510–6.
19. García-Martínez A, Hernández-Rodríguez J, Arguis P, Paredes P, Segarra M, Lozano E, et al. Development of aortic aneurysm/dilatation during the followup of patients with giant cell arteritis: A cross-sectional screening of fifty-four prospectively followed patients. Arthritis Care Res. 2008;59(3):422–30.
20. Zehr KJ, Mathur A, Orszulak TA, Mullany CJ, Schaff H V. Surgical treatment of ascending aortic aneurysms in patients with giant cell aortitis. Ann Thorac Surg. 2005 May;79(5):1512–7.
21. García-Martínez A, Arguis P, Prieto-González S, Espígol-Frigolé G, Alba MA, Butjosa M, et al. Prospective long term follow-up of a cohort of patients with giant cell arteritis screened for aortic structural damage (aneurysm or dilatation). Ann Rheum Dis. 2014;73(10):1826–32.
22. Lie JT. Aortic and extracranial large vessel giant cell arteritis: A review of 72 cases with histopathologic documentation. Semin Arthritis Rheum. 1995;24(6):422–31.
23. Gonzalez-Gay MA, Garcia-Porrua C, Piñeiro A, Pego-Reigosa R, Llorca J, Hunder GG. Aortic aneurysm and dissection in patients with biopsy-proven giant cell arteritis from northwestern Spain: A population-based study. Medicine (Baltimore). 2004;83(6):335–41.
24. Kermani TA, Warrington KJ, Crowson CS, Ytterberg SR, Hunder GG, Gabriel SE, et al. Large-vessel involvement in giant cell arteritis: A population-based cohort study of the incidence-trends and prognosis. Ann Rheum Dis. 2013;72(12):1989–94.
25. Espitia O, Blonz G, Urbanski G, Landron C, Connault J, Lavigne C, et al. Symptomatic aortitis at giant cell arteritis diagnosis: a prognostic factor of aortic event. Arthritis Res Ther. 2021 Jan;23(1):14.
26. Nuenninghoff DM, Hunder GG, Christianson TJH, McClelland RL, Matteson EL. Incidence and Predictors of Large-Artery Complication (Aortic Aneurysm, Aortic Dissection, and/or Large-Artery Stenosis) in Patients with Giant Cell Arteritis: A Population-Based Study over 50 Years. Arthritis Rheum. 2003;48(12):3522–31.
27. Maz M, Chung SA, Abril A, Langford CA, Gorelik M, Guyatt G, et al. 2021 American

College of Rheumatology/Vasculitis Foundation Guideline for the Management of Giant Cell Arteritis and Takayasu Arteritis. Arthritis Rheumatol (Hoboken, NJ). 2021 Aug;73(8):1349–65.
28. Hellmich B, Agueda A, Monti S, Buttgereit F, de Boysson H, Brouwer E, et al. 2018 Update of the EULAR recommendations for the management of large vessel vasculitis. Ann Rheum Dis. 2020;79(1):19–30.
29. Isselbacher EM, Preventza O, Hamilton Black J, Augoustides JG, Beck AW, Bolen MA, et al. 2022 ACC/AHA Guideline for the Diagnosis and Management of Aortic Disease. J Am Coll Cardiol. 2022;80(24):e223–393.
30. Muratore F, Boiardi L, Restuccia G, Cavazza A, Catanoso M, Macchioni P, et al. Relapses and long-term remission in large vessel giant cell arteritis in northern Italy: Characteristics and predictors in a long-term follow-up study. Semin Arthritis Rheum. 2020;50(4):549–58.
31. Tomelleri A, Campochiaro C, Sartorelli S, Farina N, Baldissera E, Dagna L. Presenting features and outcomes of cranial-limited and large-vessel giant cell arteritis: a retrospective cohort study. Scand J Rheumatol. 2022;51(1):59–66.

Tables and figures

Table 1: Baseline characteristics of patients with (PET positive) and without (PET negative) vascular FDG uptake ≥ grade 2

Characteristics	Total (n = 100)	PET positive (n = 74)	PET negative (n = 26)	p-value
Age at inclusion, years, mean (SD)	70 (8)	68 (7)	74 (8)	**0.001**
Sex, no. of females, n (%)	68 (68)	57 (77)	11 (42)	**0.001**
Symptom duration until diagnosis, weeks, median (IQR)	6 (3-14)	8 (4-17)	3 (2-5)	**< 0.001**
Cardiovascular risk factors/events				
○ Active or past tobacco use, n (%)	46 (49)[6]	35 (49)[2]	11 (50)[4]	0.91
○ Antihypertensive medication, n (%)	47 (47)	32 (43)	15 (58)	0.20
○ Diabetes mellitus, n (%)	5 (5)	3 (4)	2 (8)	0.60
○ Statin use, n (%)	30 (30)	20 (27)	10 (38)	0.27
○ History of stroke, n (%)	4 (2)	2 (3)	2 (8)	0.28
○ History of myocardial infarction or angor, n (%)	2 (2)	2 (3)	0 (0)	1
○ History of peripheral vascular, disease, n (%)	2 (2)	1 (1)	1 (4)	0.45
○ **Cardiovascular risk score, median (IQR)**	1 (0-2)	1 (0-2)	1 (1-2)	0.35
Symptoms at diagnosis				
○ Cranial symptoms, n (%)	76 (76)	51 (69)	25 (96)	**0.006**
○ PMR, n (%)	37 (37)	25 (34)	14 (54)	0.07
○ Constitutional symptoms, n (%)	87 (87)	70 (95)	17 (65)	**< 0.001**
○ Limb claudication, n (%)	4 (4)	4 (5)	0 (0)	0.57
Laboratory tests				
○ ESR, mm/h, median (IQR)	69 (48-105)[14]	70 (47-109)[11]	66 (52-90)[3]	0.45
○ CRP, mg/l, median (IQR)	87 (43-130)	86 (45-125)	92 (43-136)	0.70
Positive temporal artery biopsy, n (%)	49 (63)[22]	31 (60)[22]	19 (73)	0.24
Duration of follow-up, months, median (IQR)	80 (47-110)	75 (43-107)	91 (59-117)	0.26

Abbreviations: CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; FDG, fluorodeoxyglucose; IQR, interquartile range; no., number; PET, positron emission tomography; PMR, polymyalgia rheumatica; SD, standard deviation

Number of missing values are reported in superscript.

Table 2: Evolution of the aortic diameters (in mm) and volumes (in cm^3) per year in patients with (PET positive) and without (PET negative) FDG uptake ≥ grade 2 in large vessels

FDG uptake ≥ grade 2 in any large vessel						
	Crude regression coefficient (95% CI)*		**p-value**	**Adjusted regression coefficient (95% CI)°**		**p-value**
	PET negative	**PET positive**		**PET negative**	**PET positive**	
Volume of thoracic aorta	3.62 (0.69-6.57)	7.84 (6.07-9.61)	**0.02**	2.39 (-0.42-5.20)	6.82 (5.11-8.55)	**0.008**
Volume of abdominal aorta	-0.38 (-1.29-0.54)	-0.73 (-1.27- -0.20)	0.52	0.27 (-0.48-1.04)	0.12 (-0.33-0.57)	0.73
Diameter of thoracic aorta						
○ **Ascending aorta**	0.06 (-0.14-0.26)	0.34 (0.22-0.46)	**0.02**	0.10 (-0.11-0.30)	0.41 (0.29-0.53)	**0.009**
○ **Aortic arch**	0.20 (0.04-0.35)	0.31 (0.22-0.41)	0.21	0.21 (0.05-0.37)	0.35 (0.25-0.45)	0.14
○ **Descending aorta**	0.11 (-0.05-0.27)	0.34 (0.24-0.44)	**0.02**	0.11 (-0.06-0.27)	0.34 (0.25-0.45)	**0.01**
Diameter of abdominal aorta						
○ **Suprarenal aorta**	0.08 (-0.02-0.19)	0.12 (0.06-0.18)	0.53	0.07 (-0.04-0.17)	0.11 (0.04-0.17)	0.51
○ **Juxtarenal aorta**	0.12 (0.00-0.23)	0.10 (0.03-0.16)	0.78	0.14 (0.03-0.25)	0.14 (0.07-0.21)	0.98
○ **Infrarenal aorta**	0.15 (0.07-0.23)	0.07 (0.03-0.12)	0.10	0.15 (0.07-0.23)	0.08 (0.03-0.12)	0.11
FDG uptake ≥ grade 2 in thoracic aorta						
	Crude regression coefficient (95% CI)*		**p-value**	**Adjusted regression coefficient (95% CI)°**		**p-value**
	PET negative	**PET positive**		**PET negative**	**PET positive**	
Volume of thoracic aorta	4.27 (1.90-6.66)	8.35 (6.41-0.30)	**0.009**	3.11 (0.83-5.40)	7.34 (5.46-9.24)	**0.005**
Diameter of thoracic aorta						
○ **Ascending aorta**	0.11 (-0.05-0.27)	0.37 (0.24-0.50)	**0.01**	0.14 (-0.02-0.31)	0.45 (0.31-0.58)	**0.005**
○ **Aortic arch**	0.21 (0.08-0.33)	0.33 (0.23-0.43)	0.13	0.22 (0.09-0.35)	0.37 (0.27-0.48)	0.07
○ **Descending aorta**	0.19 (0.06-0.32)	0.34 (0.23-0.45)	0.09	0.18 (0.05-0.32)	0.35 (0.24-0.46)	0.06
FDG uptake ≥ grade 2 in abdominal aorta						
	Crude regression coefficient (95% CI)*		**p-value**	**Adjusted regression coefficient (95% CI)°**		**p-value**
	PET negative	**PET positive**		**PET negative**	**PET positive**	
Volume of abdominal aorta	-0.49 (-1.14-0.16)	-0.78 (-1.44- -0.14)	0.52	0.08 (-0.46-0.61)	0.23 (-0.33-0.78)	0.68
Diameter of abdominal aorta						
○ **Suprarenal aorta**	0.09 (0.01-0.16)	0.13 (0.06-0.21)	0.37	0.07 (-0.00-0.14)	0.12 (0.04-0.20)	0.33
○ **Juxtarenal aorta**	0.10 (0.02-0.18)	0.10 (0.02-0.18)	0.95	0.13 (0.05-0.20)	0.15 (0.07-0.23)	0.70
○ **Infrarenal aorta**	0.13 (0.07-0.18)	0.06 (0.01-0.12)	0.11	0.12 (0.07-0.18)	0.06 (0.00-0.12)	0.12

* Linear mixed model without adjustment for confounders

° Linear mixed model adjusted for age, sex, cardiovascular risk score, CT or PET/CT scan, and intravenous contrast

Abbreviations: 95% CI, 95% confidence interval; FDG, fluorodeoxyglucose; PET, positron emission tomography

Table 3: Association between total vascular score and the evolution in aortic diameters (mm) and volumes (cm^3)

	Crude regression coefficient of interaction term*+ (95% CI)	p-value for interaction term[1]	Adjusted regression coefficient of interaction term°+ (95% CI)	p-value for interaction term[1]
Volume of thoracic aorta	0.31 (0.09-0.52)	**0.005**	0.31 (0.11 – 0.52)	**0.003**
Volume of abdominal aorta	-0.03 (-0.10-0.04)	0.38	0.00 (-0.05 – 0.06)	0.95
Diameter of thoracic aorta				
○ **Ascending aorta**	0.02 (0.00-0.03)	**0.03**	0.02 (0.01 – 0.04)	**0.007**
○ **Aortic arch**	0.01 (0.00-0.02)	0.11	0.01 (0.00 – 0.02)	**0.05**
○ **Descending aorta**	0.01 (0.00-0.02)	**0.04**	0.01 (0.00 – 0.03)	**0.03**
Diameter of abdominal aorta				
○ **Suprarenal aorta**	0.00 (-0.00-0.01)	0.34	0.00 (-0.00 – 0.01)	0.29
○ **Juxtarenal aorta**	0.00 (-0.01-0.01)	0.59	0.00 (-0.00 – 0.01)	0.31
○ **Infrarenal aorta**	-0.01 (-0.01- -0.00)	**0.05**	-0.01 (-0.01 – -0.00)	**0.05**

* Linear mixed model without adjustment for confounders

° Linear mixed model adjusted for age, sex, cardiovascular risk score, CT or PET/CT scan, and intravenous contrast

+ Interaction between evolution in time (in year) and total vascular score

Abbreviations: 95% CI, 95% confidence interval

Table 4: Characteristics of patients with and without thoracic aneurysm

Characteristics	Total (n = 100)	Thoracic aneurysm (n = 20)	No thoracic aneurysm (n = 80)	p-value
Age at inclusion, years, mean (SD)	70 (8)	69.5 (6)	70 (8)	0.80
Sex, no. of females, n (%)	68 (68)	11 (55)	57 (71)	0.16
Symptom duration until diagnosis, week, median (IQR)	6 (3-14)	8 (6-18)	6 (3-13)	**0.04**
Cardiovascular risk factors/events at diagnosis				
○ Active or past tobacco use, n (%)	46 (49)[6]	13 (65)	33 (45)[6]	0.11
○ Antihypertensive medication, n (%)	47 (47)	10 (50)	37 (46)	0.76
○ Statin use, n (%)	30 (30)	5 (25)	25 (31)	0.58
○ Diabetes mellitus, n (%)	5 (5)	0 (0)	5 (6)	0.59
○ History of stroke, n (%)	4 (2)	1 (5)	3 (4)	1
○ History of myocardial infarction or angor, n (%)	2 (2)	0 (0)	2 (3)	1
○ History of peripheral vascular, disease, n (%)	2 (2)	0 (0)	2 (3)	1
○ Betablocker at diagnosis, n (%)	34 (34)	8 (40)	26 (33)	0.53
○ Betablocker during follow-up, n (%)	49 (49)	13 (65)	36 (45)	0.11
○ **Cardiovascular risk score, median (IQR)**	1 (0-2)	1 (1-2)	1 (0-2)	0.56
Symptoms at diagnosis				
○ Cranial symptoms, n (%)	76 (76)	12 (60)	64 (80)	0.08
○ PMR, n (%)	39 (39)	4 (20)	35 (44)	0.05
○ Constitutional symptoms, n (%)	85 (85)	19 (95)	68 (85)	0.46
○ Limb claudication, n (%)	4 (4)	1 (5)	3 (4)	1
Laboratory tests at diagnosis				
○ ESR, mm/h, median (IQR)	69 (48-105)[14]	98 (57-126)[2]	67 (43-104)[12]	**0.04**
○ CRP, mg/l, median (IQR)	87 (43-130)	121 (89-146)	78 (41 – 123)	**0.02**
Positive temporal artery biopsy, n (%)	49 (63)[22]	6 (46)[7]	44 (68)[15]	0.20
PET results				
○ Positive PET, n (%)	74 (74.0)	18 (90.0)	56 (70.0)	0.07
○ Positive PET in thoracic aorta, n (%)	60 (60.0)	16 (80.0)	44 (55.0)	**0.04**
○ TVS, median (IQR)	8 (2-14)	14 (8-16)	6 (1-14)	0.05
○ Number of vessels with FDG uptake ≥ grade 2, median (IQR)	3 (0-5)	5 (4-6)	2 (0-5)	**0.03**
○ Intensity of FDG uptake in affected vessels, median (IQR)°	2.8 (0-3)	2.8 (2.5-3.0)	2.7 (0-2.9)	**0.04**
Treatment				
○ Duration of GC treatment, months, median (IQR)	34 (24-65)[3]	44 (25-94)[1]	34 (23-60)[2]	0.32
○ Cumulative GC dose in first 2 years after diagnosis, g methylprednisolone, mean (SD)	4.7 (1.4)[6]	4.8 (1.5)	4.7 (1.3)[6]	0.73
○ Use of glucocorticoid-sparing agents during follow-up, n (%)	32 (33)[2]	7 (37)[1]	25 (32)[1]	0.66
Duration of follow-up, months, median (IQR)	80 (47-110)	107 (74-123)	71 (41-99)	**0.01**
Relapse, n (%)	68 (68)	15 (75)	53 (66)	0.10
Cardiovascular event during follow-up				
○ Aortic dissection, n (%)	0 (0)	0 (0)	0 (0)	/
○ Vascular stenosis, n (%)	14 (14)	5 (25)	9 (11)	0.15
○ Vascular surgery, n (%)	7 (7)	2 (10)	5 (6)	0.62
○ Myocardial infarction, n (%)	2 (2)	0 (0)	2 (3)	1
○ CVA, n (%)	10 (10)	3 (15)	7 (9)	0.41
○ AION, n (%)	2 (2)	0 (0)	2 (3)	1
Mortality, n (%)	13 (13)	3 (15)	10 (13)	0.72

Abbreviations: AION, anterior ischemic optic neuropathy; CRP, C-reactive protein; CVA, cerebrovascular accident; ESR, erythrocyte sedimentation rate; FDG, fluorodeoxyglucose; GC, glucocorticoids; IQR, interquartile range; no., number; PET, positron emission tomography; PMR, polymyalgia rheumatica; SD, standard deviation; TVS, total vascular score

Number of missing values are reported in superscript.

° Calculated as total vascular score divided by the number of vessels with FDG uptake ≥ grade 2

Figure 1: Association between total vascular score and the evolution in (A) volume of thoracic aorta, (B) diameter of ascending aorta, (C) diameter of aortic arch, (D) diameter of descending aorta, (E) volume of abdominal aorta, (F) diameter of suprarenal aorta, (G) diameter of juxtarenal aorta, and (H) diameter of infrarenal aorta. The linear mixed models were adjusted for age, sex, cardiovascular risk score, CT or PET/CT scan, and intravenous contrast.

Abbreviations: TVS, total vascular score