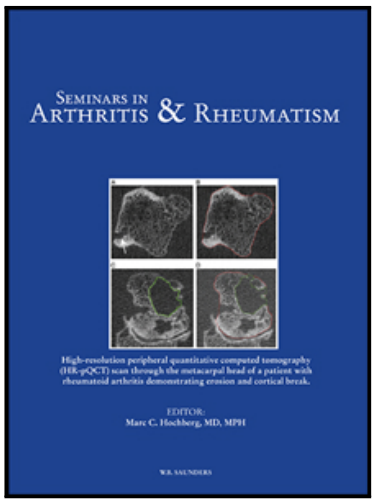

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Aortic Dilatation in Patients with Large Vessel Vasculitis: a Longitudinal Case Control Study Using PET/CT

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Running head: Aortic dilatation in LVV

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Abstract

Objective: To evaluate aortic diameter and predictors of aortic dilatation using ^{18}FDG-PET/CT in a longitudinally followed cohort of patients with large vessel vasculitis (LVV) compared with controls.

Methods: All consecutive patients with LVV who underwent at least 2 PET/CT scans between January 2008 and May 2015 were included. The first and last PET/CT study was evaluated by a radiologist and a nuclear medicine physician. Diameter and FDG uptake of the aorta was measured at 4 different levels: ascending, descending thoracic, suprarenal and infrarenal abdominal aorta. Twenty-nine age- and sex-matched patients with lymphoma who underwent at least 2 PET/CT scans in the same time interval were selected as controls.

Results: 93 patients with LVV were included in the study. In the time interval between first and last PET/CT study (median time 31 months), the diameter of the ascending, descending thoracic and suprarenal abdominal aorta significantly increased in LVV patients but not in controls. At last PET/CT, patients with LVV compared with controls had higher diameter of ascending [35.41 (5.54) vs 32.97 (4.11) mm, p=0.029], descending thoracic [28.42 (4.82) vs 25.72 (3.55) mm, p=0.007] and suprarenal abdominal aorta, mean [25.34 (7.01) vs 22.16 (3.26) mm, p=0.005] and more frequently had aortic dilatation [19% vs 3%, p=0.023]. Significant predictors of aortic dilatation were male sex [OR 7.27, p=0.001] and, only for GCA, hypertension [OR 6.30, p=0.031]. Finally, GCA patients with aortic FDG uptake grade 3 at first PET/CT, compared to those with aortic FDG uptake ≤ 2, had significantly higher aortic diameter.

Conclusions: Patients with LVV are at increased risk of aortic dilatation compared with age- and sex-matched controls. Significant predictors of aortic dilatation are male sex and, only for GCA, hypertension. GCA patients with aortic FDG uptake grade 3 are at increased risk of aortic dilatation.

Keywords: Giant cell arteritis, Takayasu arteritis, Large vessel vasculitis, Imaging, Aneurysm, PET/CT.

Abbreviations: Giant cell arteritis = GCA, Takayasu arteritis = TAK, Large-vessel vasculitides = LVV, ^{18}F fluorodeoxyglucose = ^{18}F-FDG, Positron emission tomography/computed tomography = PET/CT , computed tomography angiography = CTA, magnetic resonance angiography = MRA, color Doppler sonography = CDS, glucocorticoid = GC

Giant cell arteritis (GCA) and Takayasu arteritis (TAK) are granulomatous large-vessel vasculitides (LVV) affecting the aorta and/or its major branches that share many clinical and radiographic features [1–3]. Patients with LVV have an increased risk of developing aortic aneurysm and/or dissections [4–9], and patients with LVV who develop aortic aneurysm and/or dissection have an increased mortality compared with the general population [10–12].

Consistent predictors of aortic aneurysm/dissection in LVV are lacking. Studies with ^{18}F fluorodeoxyglucose (^{18}F-FDG) Positron Emission Tomography (PET) in LVV have shown that the aorta is involved in about 50% of the patients [13]. Some retrospective data have shown that evidence of aortic FDG uptake at GCA diagnosis may be associated with a higher risk of developing aortic complications in the long-term. In one study, patients with an increased FDG uptake in the aorta at GCA diagnosis had a significantly larger diameter of the ascending aorta and descending aorta and a significantly larger volume of the thoracic aorta at a computed tomography (CT) scan performed after a mean follow-up of 46.7 months [14]. In a more recent retrospective multicenter study, all 9 patients who developed aortic complications (dilation in all and dissection in 1 at a median time of 33 months after the GCA diagnosis) had large vessel inflammation on a previous ^{18}F-FDG-PET scan performed at diagnosis or during the follow-up [15].

The aim of the present study was to evaluate aortic diameter and predictors of aortic dilatation using PET/CT in a longitudinally followed cohort of patients with LVV compared to age- and sex-matched controls.

Material and methods

Patients

For the purpose of the present study, we selected all consecutive patients with LVV who underwent at least 2 ^{18}F-FDG PET/CT scans between January 2008 and May 2015 at our center. In all patients the diagnosis of LVV was confirmed by imaging and defined as the presence of circumferential wall thickening/wall edema with or without contrast enhancement and/or the presence of vascular

stenosis/occlusion and/or vascular dilatation/aneurysm on computed tomography angiography (CTA) or magnetic resonance angiography (MRA); the presence of long segments of smooth arterial stenosis or smooth tapered occlusion and/or vascular dilatation/aneurysm on angiography; the presence of vascular ^{18}F-FDG uptake compatible with vasculitis on FDG-PET; the presence of a hypo-isoechoic circumferential wall thickening not attributed to atherosclerotic changes on color Doppler sonography (CDS) [16]. Patients younger than 50 years at symptoms' onset were classified as TAK and those older than 50 years as GCA.

Twenty-nine age- and sex-matched patients with lymphoma who underwent at least 2 ^{18}F-FDG PET/CT scans in the same time interval were selected as controls. Patients with isolated aortitis, retroperitoneal fibrosis and previous aortic surgery were excluded from the study.

Erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) levels were measured, and a complete physical examination was performed by a trained rheumatologist in all patients at each PET/CT scan examination.

The available medical records of study participants were reviewed from the date of LVV diagnosis (first PET/CT for controls) to the end of the study period (31 May 2015). Information about demographics, cardiovascular risk factors (hypertension, hypercholesterolemia, tobacco smoking, diabetes mellitus and cardiovascular events, defined according to criteria previously reported by our group [17]), clinical manifestations, histology, imaging and laboratory finding, glucocorticoid (GC) dose and therapeutic outcomes were collected at diagnosis and at each follow-up visit.

Disease activity was evaluated using the Kerr/National Institutes of Health index, which assesses four items: constitutional manifestations, raised ESR and/or CRP, clinical manifestations of vascular ischemia and angiographic features indicative of vasculitis [18]. Disease was defined as active in the presence of at least two new or worsened items in the previous 3 months. For the purposes of this study, to determine vessel lumen changes we used CTA or MRA instead of conventional digital subtraction angiography. In patients with GCA, disease was considered active

also in the presence of unequivocal cranial and/or visual symptoms and/or polymyalgia rheumatica associated with elevation of ESR or CRP.

^{18}F Fluorodeoxyglucose Positron Emission Tomography/Computed Tomography

In the study period all PET/CT scans were performed using a standardized protocol: PET/CT images were acquired using a hybrid PET/CT machine (Discovery, GE) with 3.30-minute emission scan/bed and CT-attenuation correction. All subjects were kept fasting for ≥ 4 hours before ^{18}F-FDG injection (37 MBq of ^{18}F-FDG per 13 kilograms of patient weight). Blood glucose levels before tracer injection were ≤ 200 mg/ml in all cases. Mean time from injection to acquisition was 60 minutes. Free breathing, low dose, non-contrast enhanced helical CT was carried out for PET coregistration. Whole-body ^{18}F-FDG PET/CT scan was performed from the base of skull to the proximal femora. Transverse, coronal, and sagittal images were reconstructed using standard company reconstruction algorithms.

The first and last ^{18}F-FDG PET/CT study of each patient was independently evaluated by a radiologist (non-contrast enhanced CT-attenuation correction study) and a nuclear medicine physician (PET study).

The diameter of the aorta was measured by the radiologist in a transverse plane at four different levels (ascending aorta, descending thoracic aorta, suprarenal and infrarenal abdominal aorta). Measurements were taken at the first third of the ascending aorta, distal to the aortic root (Figure 1A); at the first part of the thoracic descending aorta, distal to the isthmus (Figure 1B); at the first part of the suprarenal abdominal aorta, distal to the transition zone at the level of the diaphragm (Figure 1C); and at the first part of the infrarenal abdominal aorta, distal to the renal arteries (Figure 1D). Aortic dilatation was defined by a diameter > 40 mm in the ascending aorta, ≥ 40 mm in the thoracic descending aorta and ≥ 30 mm in the abdominal aorta [19].

Aortic ^{18}F-FDG uptake was evaluated visually and semi-quantitatively by the nuclear medicine physician at the same aortic levels. A visual score was assigned to each aortic segment using a 4-

point scale: 0 = no uptake, 1 = uptake lower than the liver, 2 = uptake similar to the liver, and 3 = uptake higher than the liver [20].

To evaluate the accuracy of the free breathing, low-dose, non-contrast enhanced CT-attenuation correction study for the measurement of aortic diameters, 10 LVV patients who underwent aortic CTA within one month from PET/CT study were selected. The diameter of the aorta was measured by the radiologist on CTA and PET/CT studies at the four defined levels (figure 1A-H).

The study was approved by the Reggio Emilia Provincial Ethics Committee and informed consent was obtained from all patients.

Statistical analysis

Continuous data were described as mean and standard deviation (mean ± SD) or median and interquartile range (Q1, Q3), and categorical variables as absolute frequencies and percentages. Continuous variables were compared by using t-test and paired t-tests or Mann-Whitney and Wilcoxon signed rank tests when the distributions were skewed. Comparison of categorical variables was performed by using chi-square or Fischer's exact test, as appropriate. A univariate logistic regression model was used to identify characteristics at diagnosis that increased the odds of aortic dilatation. Univariate age-adjusted odds ratio (ORs) and 95% confidence intervals (95% CIs) were reported. Agreement between methods was assessed using intraclass correlation coefficients (ICC's; two-way random, absolute agreement) and Bland-Altman plots (for which 95% limits of agreement were calculated). All tests were two-sided; significance was defined at $p < 0.05$. Statistical analysis was performed using SPSS version 25 (IBM Statistics, Armonk, NY: IBM Corp, USA).

Results

Study cohorts

Ninety-three patients with LVV underwent at least 2 ^{18}F-FDG PET/CT scans in the study period (January 2008 to May 2015) and were included. LVV was diagnosed by PET in 38 patients (40%), CTA in 24 (26%), MRA in 11 (12%), CDS in 10 (11%) and conventional angiography in 10 (11%). Fifty-two patients (56%) were classified as GCA and 41 (44%) as TAK. ACR classification criteria for GCA were satisfied in 18/52 (35%) GCA patients, and ACR classification criteria for TAK in 35/39 (90%) TAK patients [21,22]. Seven patients had symptoms' onset between 41 and 50 years of age and were classified as TAK. Five of these 7 patients met the ACR classification criteria for TAK, and none the ACR classification for GCA. 18 patients with GCA underwent temporal artery biopsy, which was positive for GCA in 7 (39%). At first PET/CT scan, 48 of 93 patients (52%) had newly-diagnosed LVV (35 GCA and 13 TAK) and 42 patients (16 GCA and 26 TAK) had a median (Q1, Q3) disease duration of 34 (13, 96) months. For the remaining 3 patients (1 GCA and 2 TAK) data on disease duration was not available.

Twenty-nine age and sex matched patients with lymphoma who underwent at least 2 ^{18}F-FDG PET/CT scans in the same time interval were selected as controls.

None of the 29 controls had evidence of aortic FDG uptake at PET/CT. At first PET/CT study 42/76 (55%) of LVV patients had active disease according to the modified Kerr/NIH criteria and the presence of GCA manifestations (see methods for details). Comparisons between patients with LVV and controls are reported in Table 1. There were no differences in the frequencies of the cardiovascular risk factors evaluated between the two study groups. At first PET/CT study, mean diameters of descending thoracic and suprarenal abdominal aorta were significantly higher in LVV patients compared with controls; the difference in the proportion of patients with aortic dilatation did not reach statistical significance (18% vs 3%, p=0.069). At last PET/CT, patients with LVV

compared with controls had higher diameter of ascending, descending thoracic and suprarenal abdominal aorta and more frequently had aortic dilatation (19% vs 3%, p=0.023).

In the time interval between first and last PET/CT study, the mean diameter of the ascending, descending thoracic and suprarenal abdominal aorta significantly increased in LVV patients but not in controls. Comparisons of aortic diameter at first vs last PET/CT, mean (SD) mm: ascending aorta: 34.81 (5.42) vs 35.41 (5.54), p<0.0001 in LVV and 32.88 (4.11) vs 32.97 (4.11), p=0.113 in controls; descending thoracic aorta: 28.07 (4.40) vs 28.42 (4.82), p=0.017 in LVV and 25.60 (3.59) vs 25.72 (3.55), p=0.187 in controls; suprarenal abdominal aorta: 24.86 (5.59) vs 25.34 (7.01), p=0.013 in LVV and 22.20 (3.19) vs 22.16 (3.26), p=0.707 in controls).

All the results remained unchanged when the analysis were restricted to the 48 patients with newly-diagnosed LVV (Table S1).

Predictors of aortic dilatation

At last PET/CT study, 18 of the 93 LVV patients (19%) had aortic dilatation. All but one of these 18 patients had already evidence of aortic dilatation at first PET/CT study. The most common site of aortic dilatation was ascending aorta for both GCA and TAK patients (10 and 5 cases, respectively). Two patients had thoraco-abdominal aortic dilatation (1 GCA and 1 TAK) and one GCA patients had dilatation of the descending thoracic aorta.

Comparisons between patients with and without aortic dilatation at last PET/CT are reported in Table 2. At univariate analysis adjusted for age, the only significant predictor of aortic dilatation was male sex [OR (95% CI) 7.273 (2.353 – 22.481), p=0.001]. There was a trend for hypertension as predictor [OR (95% CI) 2.850 (0.908 – 8.950), p=0.073]. Aortic FDG uptake ≥ grade 2 or grade 3, disease activity, inflammatory markers levels and GC doses at both first and last PET/CT study, the presence of other cardiovascular risk factor and disease relapses were not associated with an increased risk of aortic dilatation.

The results remained unchanged when the analysis were restricted to the 48 newly-diagnosed LVV patients (Table S2).

When the analysis was restricted to the 52 GCA patients (12 with and 40 without aortic dilatation), significant predictors of aortic dilatation were male sex [OR (95% CI) 6.600 (1.615 – 26.977), p=0.009] and hypertension [OR (95% CI) 6.300 (1.187 – 33.443), p=0.031]. When the analysis was restricted to the 41 TAK patients (6 with and 35 without aortic dilatation), the only significant predictors of aortic dilatation was male sex [OR (95% CI) 7.750 (1.148 – 52.297), p=0.036].

At first PET/CT study, 55/93 patients (59%) had aortic FDG uptake ≥ grade 2 (42 GCA and 13 TAK patients) and 31/93 (33%) grade 3 (26 GCA and 5 TAK patients). Interestingly, GCA patients with aortic FDG uptake grade 3 at first PET/CT, compared to those with aortic FDG uptake ≤ 2, had significantly higher aortic diameter at all 4 aortic levels evaluated at both first and last PET/CT study (Table 3). Furthermore, GCA patients with aortic FDG uptake grade 3 at first PET/CT, compared to those with aortic FDG uptake ≤ 2, had more frequent active disease, higher level of inflammatory markers and less frequently were on GC therapy at first PET/CT (Table 3). This difference was not found comparing GCA patients with aortic FDG uptake grade ≥ 2 to those with aortic FDG uptake < 2 (Table S3), nor comparing TAK patients with aortic FDG uptake grade 3 with those with uptake ≤ 2 (data not shown because of low number of TAK patients with FDG uptake grade 3) and TAK patients with aortic uptake ≥ 2 with those with uptake < 2 (Table S4).

Comparisons between GCA and TAK patients

At first PET/CT study, GCA compared with TAK patients had shorter disease duration, more frequent active disease, aortic FDG uptake ≥ grade 2 and grade 3 and higher level of inflammatory markers. GCA patients had higher aortic diameter at all 4 levels evaluated in both first and last PET/CT study (Table 4). However, there were no differences in the proportion of patients with aortic dilatation at both first and at last PET/CT. When the analysis was restricted to the 48 newly-diagnosed LVV patients (35 GCA and 13 TAK), 23% of GCA patients had aortic dilatation at first

PET/CT and 26% at last PET/CT versus none of TAK patients at both first and last PET/CT, p=0.088 and p=0.090, respectively.

Agreement between PET/CT and CTA.

Agreement between low-dose, non-contrast enhanced CT-attenuation correction study and CTA for the measurement of aortic diameters in the10 LVV patients evaluated was excellent, with an ICC ranging between 0.998 and 0.999 (all p<0.0001), (table 5). Bland-Altman plot confirmed excellent agreement at all 4 aortic levels evaluated (figure S1).

Discussion

In the present study, patients with LVV had higher diameter of the thoracic aorta and higher frequency of aortic dilatation compared with age- and sex-matched controls. These differences were already present at first PET/CT, but became statistically stronger at last PET/CT study, after a median (Q1, Q3) follow-up of 31 (15, 52) months. In this time interval, diameter of the ascending, descending thoracic and suprarenal abdominal aorta significantly increased in LVV patients but not in controls. At last PET/CT, aortic dilatation was found in 19% of LVV patients and 3% of controls, the difference being statistically significant. In all but one LVV patient aortic dilatation was already present at first PET/CT study.

Our study confirms the findings of previous reports on GCA. In a prospective study, Agard et al reported a higher prevalence of aortic dilatation in 22 patients with newly-diagnosed, biopsy-proven GCA (23%) compared to 22 age- and sex-matched controls (9%), a frequency close to that reported by our study [23]. Similarly, Garcia-Martinez et al reported higher diameter of the descending aorta and more frequent aortic dilatation (22% vs 7%) in 54 biopsy-proven GCA patients cross-sectionally evaluated after a median follow-up of 5.4 years compared to 28 age and sex-matched

controls [24]. To our knowledge no previous studies compared aortic diameter between TAK patients and age and sex-matched controls.

Aortic dilatation has been reported both in the early and late course of GCA (15-23% of newly diagnosed GCA patients and 22.2% and 33.3% of patients after a median disease duration of 5.4 and 10.3 years, respectively) [19,23–25]. Similarly, aortic dilatation has been reported in a variable proportion of TAK patients, ranging from 4 to 45% [6–8,26,27]. In a recent study reporting the results of 1372 newly diagnosed TAK patients from a Japanese nationwide registration form, aortic aneurisms were present in 15% of TAK patients and aortic dissection in 1.9% [7].

At last PET/CT study, after a median time of 45 months from diagnosis, we found aortic dilatation in 12/52 (23%) of GCA and 6/41 (15%) of TAK patients, a frequency close to that reported by previous studies on GCA and TAK. Confirming previous reports, the most common site of aortic dilatation was ascending thoracic aorta for both GCA and TAK patients. Hemodynamic mechanisms and anatomical features may account for the ascending aorta predisposition to aneurysm (higher blood pressure, density of vasa vasorum, collagen and elastin fibers) [24]. When the analysis was restricted to the 48 newly-diagnosed LVV patients (35 GCA and 13 TAK), aortic dilatation was found in 23% of GCA patients and in none of TAK patients. Taken together, these findings suggest that aortic dilatation could occur both in the early and late course of GCA, while it seems a later complication in TAK. Mechanisms underlying the response of the artery to injury are not fully understood, and different pathophysiologic mechanisms (beyond age) may account for the variable response to large vessel inflammation in GCA and TAK.

Different retrospective and prospective studies evaluated the risk factors for aortic dilatation in GCA patients. Reported predictors were male gender [14,19,24], younger age at diagnosis [28], increasing time since diagnosis [14], earlier suspension of prednisolone [24], hypertension [28], hyperlipidemia [29], lack of hyperlipidemia [24], coronary artery disease [29], increased aortic FDG uptake by PET at GCA diagnosis [14], aortic murmur due to regurgitation at GCA diagnosis

[29], extracranial large vessel involvement [16,30], a combination of polymyalgic symptoms and elevated laboratory markers of inflammation at GCA diagnosis [28], and lower ESR and higher hemoglobin concentration at the time of aneurysm screening [24]. Studies evaluating risk factors for aortic dilatation in TAK patients are lacking, and the only reported predictor was male gender [7,8].

As suggested by most studies, gender-associated factors may play a significant role. In agreement with these findings, the strongest predictor of aortic dilatation in the present study was male sex for both GCA and TAK patients. Male predominance in susceptibility to aortic aneurysms has also been demonstrated in experimental settings in rats [31,32].

In the present study hypertension was a strong predictor of aortic dilatation in GCA patients, confirming the results reported by Gonzalez-Gay et al in a retrospective study of 210 biopsy-proven GCA patients from Lugo, Spain [28]. Contrary to previous reports, we did not find any association between aortic dilatation and the other cardiovascular risk factors evaluated (smoking, hypercholesterolemia, diabetes mellitus, cardiovascular events). Furthermore, we did not find any association between aortic dilatation and age, clinical manifestations and inflammatory markers at GCA diagnosis, aortic FDG uptake, disease activity and inflammatory markers at both first and last PET/CT study, and disease relapses and GC therapy during the course of the disease.

Interestingly, GCA patients with aortic FDG uptake grade 3 at first PET/CT, compared to those with aortic FDG uptake ≤ 2, had significantly higher aortic diameter at all 4 aortic levels evaluated at both first and last PET/CT study, suggesting that an initial intense aortic inflammation may induce early aortic dilatation in GCA patients. These differences were not found when we compared GCA patients with aortic FDG uptake grade ≥ 2 to those with aortic FDG uptake < 2, nor in TAK patients independently from FDG grade uptake. Our results partially confirm those reported by Blockmans et al, in which patients with aortic FDG uptake grade ≥ 2 at GCA diagnosis had a significantly larger diameter of the ascending aorta and descending aorta and a significantly larger volume of the thoracic aorta at a CT scan performed after a mean follow-up of 46.7 months [14].

Differently from our study, Blockmans et al did not perform baseline aortic CT scan, and therefore they were not able to define when aortic dilatation occurred in the disease course. PET is particularly valuable in diagnosing LVV, while its role is less well established in evaluating disease activity and predicting the course of the disease and its complications. While FDG uptake grade 3 is considered relatively specific for active vasculitis, the meaning of lower grade vascular FDG uptake, particularly after treatment, is still unclear [33]. Our study confirms that GCA patients with an initial more intense aortic inflammation (FDG uptake grade 3) are at increased risk of aortic dilatation.

In the present study, in all but one newly-diagnosed GCA patients who had aortic dilatation at last PET/CT, aortic dilatation was already evident at first PET/CT study. Furthermore, in the time interval between first and last PET/CT study, diameter of the ascending, descending thoracic and suprarenal abdominal aorta significantly increased. These data suggest that the inflammatory damage leading to aortic dilatation may occur in the early phase of the disease, and continue thereafter. Population-based studies have shown that the incidence of aortic aneurysm/dissection increases 5 years after GCA diagnosis and continues to increase thereafter [10]. The short follow-up duration of our study may explain the low incidence of new aortic dilatation found between the two PET/CT study (only 1 patient) despite the increased growth rate of aortic diameter showed in GCA patients. GCA patients with risk factors for aortic dilatation (male gender, hypertension, more intense aortic inflammation) may have an earlier damage of the elastic fibers and muscular layer, or a less efficient vascular repair or remodeling after injury that contribute to progressive arterial dilatation [34]. If prospective studies with longer follow-up confirm these findings, systematic screening for aortic dilatation at GCA diagnosis could allow us to identify those patients at higher risk of aortic aneurysm.

Special attention for aortic dilatation should be paid in some patients diagnosed as having isolated polymyalgia rheumatica (PMR). In this regard, PMR and GCA are often overlapping conditions and ^{18}F-FDG-PET/CT scan studies have disclosed that at least a third of patients with PMR have LVV

involvement [35]. The frequency is even higher in patients with persistent PMR despite glucocorticoid therapy associated to other less common features [36]. Information on long-term studies assessing the risk of aortic aneurysmal disease in these patients is scarce. Therefore, prospective follow-up studies looking for progression of aortic dilatation should also be considered in these patients.

Finally, our study confirms that the ACR criteria for GCA are inadequate for the classification of patients with LV-GCA, and that TAB is positive in less than 50% of patients with LV-GCA [16,37].

Our study has several limitations. The most important potential limitation is the use of free-breathing, low-dose, non-contrast enhanced CT-attenuation correction study for the evaluation of aortic diameters. To evaluate the accuracy of this method, aortic diameter was measured by the radiologist on CTA and PET/CT studies of 10 LVV patients. Agreement between the two imaging modalities was excellent (Table 5 and Figure S1). Another potential limitation is the heterogeneity of the study cohort included regarding diagnosis (56% GCA and 44% TAK), disease status at first PET/CT (55% active and 45% inactive) and disease duration at first PET/CT study (52% newly diagnosed and 48% longstanding disease with a variable disease duration). This heterogeneity could have decreased the strength of our conclusions. To overcome this limitation different sub-analyses were performed: analyses restricted to GCA and TAK (see results and Table 4), to active and inactive disease according to aortic FDG uptake (Table 3, S3 and S4) and to newly-diagnosed LVV patients (Table S1 and S2). Reassuringly, the main findings of the study remained unchanged. Other important limitations are the short follow-up duration (mean time interval between first and last PET/CT 35 months) and the retrospective design of the study. Prospective studies with longer follow-up are therefore needed. However, our study has a number of strengths. The most important are the monocentric design of the study with the inclusion of consecutive LVV patients homogeneously evaluated and the careful analysis of the imaging by a dedicated radiologist and nuclear medicine physician.

In conclusion, patients with LVV (both GCA and TAK) have an increased growth rate of aortic diameter and are at increased risk of aortic dilatation compared with age- and sex-matched controls. Aortic dilatation may be an early manifestation of the disease in GCA. Significant predictors of aortic dilatation are male sex and, only for GCA, hypertension and a more intense aortic inflammation at FDG PET/CT.

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Table 1. Comparisons between patients with LVV and age and sex matched controls.

Variable	LVV (n=93)	Controls (n=29)	p value
Age at first PET-CT, mean (SD) years	55.4 (17.6)	53.9 (13.1)	0.294
Female	72/93 (77.4%)	18/29 (62.1)	0.101
Tobacco smoking	19/88 (21.6%)	5/24 (20.8%)	0.936
Hypertension	44/87 (50.6%)	9/24 (35.7%)	0.183
Hypercholesterolemia	17/88 (19.3%)	4/24 (16.7%)	1.000
Diabetes mellitus	5/93 (5.4%)	2/29 (6.9%)	0.670
Cardiovascular Events	30/90 (33.3%)	5/25 (20%)	0.200
First PET-CT			
Aortic dilatation	17/93 (18.3%)	1/29 (3.4%)	0.069
Diameter ascending aorta, mean (SD) mm	34.81 (5.42)	32.88 (4.11)	0.062
Diameter descending thoracic aorta, mean (SD) mm	**28.07 (4.40)**	**25.60 (3.59)**	**0.012**
Diameter suprarenal abdominal aorta, mean (SD) mm	**24.86 (5.59)**	**22.20 (3.19)**	**0.008**
Diameter infrarenal abdominal aorta, mean (SD) mm	18.11 (4.34)	16.93 (2.92)	0.202
Time interval between first and last PET-CT, median (Q1, Q3) months	31 (14, 57)	30 (16, 43)	1.000
Last PET-CT			
Aortic dilatation	**18/93 (19.4%)**	**1/29 (3.4%)**	**0.023**
Diameter ascending aorta, mean (SD) mm	**35.41 (5.54)**	**32.97 (4.11)**	**0.029**
Diameter descending thoracic aorta, mean (SD) mm	**28.42 (4.82)**	**25.72 (3.55)**	**0.007**
Diameter suprarenal abdominal aorta, mean (SD) mm	**25.34 (7.01)**	**22.16 (3.26)**	**0.005**
Diameter infrarenal abdominal aorta, mean (SD) mm	18.15 (4.21)	16.76 (2.82)	0.119

Except where indicated otherwise, values are the number of patients who were positive/number of patients for whom data were available (%).

Table 2. Comparisons between patients with aortic dilatation at last PET/CT and those without

Variable	Dilated (n=18)	Not dilated (n=75)	p value
Age at diagnosis, mean (SD) years	58.1 (17.1)	52.0 (19.2)	0.269
Female	**8/18 (44.4%)**	**64/75 (85.3%)**	**<0.0001**
GCA	12/18 (66.7%)	40/75 (53.3%)	0.306
Tobacco smoking	5/17 (29.4%)	14/71 (19.7%)	0.511
Hypertension	12/17 (70.6%)	32/70 (45.7%)	0.103
Hypercholesterolemia	1/17 (5.9%)	16/71 (22.5%)	0.175
Diabetes mellitus	0/18 (0.0%)	5/75 (6.7%)	0.579
Cardiovascular Events	7/18 (38.9%)	23/72 (31.9)	0.576
Time from symptoms onset to diagnosis, median (Q1, Q3) months	6.50 (2.0, 16.0)	7.0 (3.0, 23.5)	0.942
New diagnosis	9/18 (50%)	39/72 (54.2%)	0.751
ESR at LVV diagnosis mean (SD) mm/h	82.9 (28.5)	76.8 (35.1)	0.636
CRP at LVV diagnosis mean (SD) mg/dL	9.05 (7.17)	6.86 (6.33)	0.334
Time from diagnosis to first PET-CT, median (Q1, Q3), months	2.5 (0.0, 57.0)	0.0 (0.0, 24.5)	0.958
First PET-CT			
GC therapy	7/17 (41.2%)	35/68 (51.5%)	0.448
PD dose mean (SD) mg/day	12.86 (5.48)	12.29 (10.88)	0.217
Active disease#	9/16 (56.2%)	33/60 (55.20%)	0.929
Elevated inflammatory markers	14/17 (82.4%)	51/70 (72.9%)	0.543
ESR mean (SD) mm/h	54.3 (37.9)	53.2 (36.3)	0.877
CRP mean (SD) mg/dL	4.42 (6.15)	3.33 (4.69)	0.378
Aortic FDG-uptake ≥ grade 2	12/18 (66.7%)	43/75 (57.3%)	0.469
Aortic FDG-uptake grade 3	8/18 (44.4%)	23/75 (30.7%)	0.265
Diameter ascending aorta, mean (SD) mm	**42.14 (4.83)**	**33.05 (3.87)**	**<0.0001**
Diameter descending thoracic aorta, mean (SD) mm	**32.91 (4.68)**	**26.91 (3.46)**	**<0.0001**
Diameter suprarenal abdominal aorta, mean (SD) mm	**30.85 (7.19)**	**23.43 (4.03)**	**<0.0001**
Diameter infrarenal abdominal aorta, mean (SD) mm	**21.39 (6.64)**	**17.33 (3.18)**	**0.002**
Time interval between first and last PET-CT, median (Q1, Q3) months	43.0 (22.0, 70.0)	30.0 (13.5, 47.0)	0.402
Time interval between symptoms onset and last PET-CT, median (Q1, Q3) months	41.5 (27.5, 149.3)	55.5 (27.8, 101.0)	0.767
Last PET-CT			
GC therapy	10/15 (66.7%)	41/61 (67.2%)	1.000
PD dose mean (SD) mg/day	7.63 (3.25)	6.34 (5.07)	0.074
Active disease#	2/13 (15.4%)	4/54 (7.4%)	0.329
Elevated inflammatory markers	11/16 (68.8%)	30/63 (47.6%)	0.166
ESR mean (SD) mm/h	26.3 (20.1)	26.6 (20.0)	0.872
CRP mean (SD) mg/dL	1.12 (1.45)	0.98 (1.11)	0.694
Relapses	4/7 (57.1%)	10/36 (27.8%)	0.190
Aortic FDG-uptake ≥ grade 2	4/18 (22.2%)	12/75 (16.0%)	0.503
Aortic FDG-uptake grade 3	1/18 (5.6%)	1/75 (1.3%)	0.351

Variable	Dilated (n=18)	Not dilated (n=75)	p value
Diameter ascending aorta, mean (SD) mm	**43.00 (5.56)**	**33.58 (3.70)**	**<0.0001**
Diameter descending thoracic aorta, mean (SD) mm	**33.62 (5.55)**	**27.17 (3.70)**	**<0.0001**
Diameter suprarenal abdominal aorta, mean (SD) mm	**32.18 (11.15)**	**23.70 (4.29)**	**<0.0001**
Diameter infrarenal abdominal aorta, mean (SD) mm	**21.10 (6.17)**	**17.45 (3.27)**	**0.003**

Except where indicated otherwise, values are the number of patients who were positive/number of patients for whom data were available (%).

Disease activity was evaluated using the modified Kerr/NIH criteria and the presence of GCA manifestations (see methods for details)

Table 3. Comparisons between GCA patients with aortic FDG-uptake grade 3 at first PET/CT and those with aortic FDG-uptake ≤ grade 2

Variable	FDG-uptake grade 3 (n=26)	FDG-uptake ≤ grade 2 (n=26)	p value
Age at diagnosis, mean (SD) years	65.3 (7.5)	67.9 (9.8)	0.417
Female	18/26 (69.2%)	20/26 (76.9%)	0.532
Time from symptoms onset to diagnosis, median (Q1, Q3) months	4 (2, 6.5)	6 (2, 13)	0.357
New diagnosis	21/26 (80.8%)	14/25 (56%)	0.075
Time from diagnosis to first PET-CT, median (Q1, Q3), months	0 (0, 0)	0 (0, 11)	0.053
First PET-CT			
GC therapy	**6/24 (25%)**	**14/23 (60.9%)**	**0.013**
PD dose mean (SD) mg/day	16.25 (14.49)	12.32 (10.87)	0.353
Active disease#	**20/20 (100%)**	**12/20 (60%)**	**0.003**
Elevated inflammatory markers	**23/24 (95.8%)**	**17/23 (73.9%)**	**0.048**
ESR mean (SD) mm/h	**81.7 (32.7)**	**57.4 (38.1)**	**0.029**
CRP mean (SD) mg/dL	**6.18 (6.00)**	**3.22 (4.44)**	**0.008**
Aortic dilatation	8/26 (30.8%)	3/26 (11.5%)	0.173
Diameter ascending aorta, mean (SD) mm	**36.92 (4.34)**	**34.84 (4.80)**	**0.032**
Diameter descending thoracic aorta, mean (SD) mm	**31.43 (4.23)**	**28.27 (3.40)**	**0.004**
Diameter suprarenal abdominal aorta, mean (SD) mm	**28.51 (4.79)**	**24.98 (3.02)**	**0.001**
Diameter infrarenal abdominal aorta, mean (SD) mm	**21.09 (5.33)**	**18.16 (2.69)**	**0.013**
Time interval between first and last PET-CT, median (Q1, Q3) months	29.5 (14, 49.3)	24.5 (14, 42)	0.782
Time interval between symptoms onset and last PET-CT, median (Q1, Q3) months	33 (21, 45.5)	40.5 (25, 71)	0.647
Last PET-CT			
GC therapy	13/21 (61.9%)	16/21 (76.2%)	0.505
PD dose mean (SD) mg/day	6.54 (4.87)	5.23 (3.20)	0.812
Active disease#	3/19 (15.8%)	2/21 (9.5%)	0.654
Elevated inflammatory markers	12/22 (54.5%)	13/23 (56.5%)	0.894
ESR mean (SD) mm/h	29.5 (21.8)	30.0 (22.8)	0.981
CRP mean (SD) mg/dL	1.12 (1.39)	1.15 (1.23)	0.760
Relapses	6/18 (33.3%)	4/14 (28.6%)	1.000
Aortic FDG-uptake ≥ grade 2	8/26 (30.8%)	3/26 (11.5%)	0.173
Aortic FDG-uptake grade 3	2/26 (7.7%)	0/26 (0%)	0.490
Aortic dilatation	8/26 (30.8%)	4/26 (15.4%)	0.324

Variable	FDG-uptake grade 3 (n=26)	FDG-uptake ≤ grade 2 (n=26)	p value
Diameter ascending aorta, mean (SD) mm	**37.22 (4.43)**	**35.22 (5.87)**	**0.012**
Diameter descending thoracic aorta, mean (SD) mm	**32.23 (4.88)**	**28.68 (3.81)**	**0.004**
Diameter suprarenal abdominal aorta, mean (SD) mm	**30.02 (8.85)**	**25.18 (3.20)**	**0.001**
Diameter infrarenal abdominal aorta, mean (SD) mm	**20.95 (4.96)**	**18.44 (3.24)**	**0.017**

Except where indicated otherwise, values are the number of patients who were positive/number of patients for whom data were available (%).

Disease activity was evaluated using the modified Kerr/NIH criteria and the presence of GCA manifestations (see methods for details)

Table 4. Comparisons between GCA and TAK patients

Variable	GCA (n=52)	TAK (n=41)	p value
Age at diagnosis, mean (SD) years	**66.6 (8.7)**	**35.7 (13.5)**	**<0.0001**
Female	38/52 (73.1%)	34/41 (82.9%)	0.259
Tobacco smoking	**17/48 (35.4%)**	**2/40 (5%)**	**0.001**
Hypertension	24/47 (51.1%)	20/40 (50%)	0.921
Hypercholesterolemia	8/47 (17%)	9/41 (22%)	0.559
Diabetes mellitus	3/52 (5.8%)	2/41 (4.9%)	1.000
Cardiovascular Events	**25/49 (51%)**	**5/41 (12.2%)**	**<0.0001**
Time from symptoms onset to diagnosis, median (Q1, Q3) months	**4.0 (2.0, 7.5)**	**24.0 (8.0, 103.0)**	**<0.0001**
New diagnosis	**35/51 (68.6%)**	**13/39 (33.3%)**	**0.001**
Time from diagnosis to first PET-CT, median (Q1, Q3), months	**0.00 (0.0, 5.0)**	**21.0 (0.0, 87.0)**	**<0.0001**
First PET-CT			
GC therapy	20/47 (42.6%)	22/38 (57.9%)	0.160
PD dose mean (SD) mg/day	13.5 (11.81)	11.36 (8.48)	0.970
Active disease#	**32/40 (80%)**	**10/36 (27.8%)**	**<0.0001**
Elevated inflammatory markers	**40/47 (85.1%)**	**25/40 (62.5%)**	**0.016**
ESR mean (SD) mm/h	**69.8 (37.1)**	**34.2 (24.3)**	**<0.0001**
CRP mean (SD) mg/dL	**4.7 (5.4)**	**2.2 (4.0)**	**0.001**
Aortic FDG-uptake ≥ grade 2	**42/52 (80.8%)**	**13/41 (31.7%)**	**<0.0001**
Aortic FDG-uptake grade 3	**26/52 (50.0%)**	**5/41 (12.2%)**	**<0.0001**
Aortic dilatation	11/52 (21.2%)	6/41 (14.6%)	0.419
Diameter ascending aorta, mean (SD) mm	**35.89 (4.66)**	**33.44 (6.05)**	**0.035**
Diameter descending thoracic aorta, mean (SD) mm	**29.86 (4.13)**	**25.80 (3.65)**	**<0.0001**
Diameter suprarenal abdominal aorta, mean (SD) mm	**26.74 (4.34)**	**22.49 (6.13)**	**<0.0001**
Diameter infrarenal abdominal aorta, mean (SD) mm	**19.63 (4.44)**	**16.19 (3.39)**	**<0.0001**
Time interval between first and last PET-CT, median (Q1, Q3) months	26.5 (15.5, 43.5)	32.0 (14.0, 67.0)	0.354
Time interval between symptoms onset and last PET-CT, median (Q1, Q3) months	**36 (24.5, 57.5)**	**132 (60, 225)**	**<0.0001**
Last PET-CT			
GC therapy	29/42 (69%)	22/34 (64.7%)	0.689
PD dose mean (SD) mg/day	5.82 (4.01)	7.61 (5.55)	0.125
Active disease#	5/40 (12.5%)	1/27 (3.7%)	0.389
Elevated inflammatory markers	25/45 (55.6%)	16/34 (47.1%)	0.454
ESR mean (SD) mm/h	29.7 (22.1)	22.4 (16.2)	0.148
CRP mean (SD) mg/dL	1.14 (1.29)	0.83 (0.99)	0.094

Variable	GCA (n=52)	TAK (n=41)	p value
Relapse	10/32 (31.2%)	4/11 (36.4%)	1.000
Aortic FDG-uptake ≥ grade 2	11/52 (21.2%)	5/41 (12.2%)	0.196
Aortic FDG-uptake grade 3	2/52 (3.8%)	0/41 (0%)	0.310
Aortic dilatation	12/52 (23.1%)	6/41 (14.6%)	0.306
Diameter ascending aorta, mean (SD) mm	36.22 (5.25)	34.37 (5.80)	0.173
Diameter descending thoracic aorta, mean (SD) mm	**30.46 (4.69)**	**25.83 (3.62)**	**<0.0001**
Diameter suprarenal abdominal aorta, mean (SD) mm	**27.60 (7.02)**	**22.47 (5.92)**	**<0.0001**
Diameter infrarenal abdominal aorta, mean (SD) mm	**19.70 (4.34)**	**16.20 (3.12)**	**<0.0001**

Except where indicated otherwise, values are the number of patients who were positive/number of patients for whom data were available (%).

Disease activity was evaluated using the modified Kerr/NIH criteria and the presence of GCA manifestations (see methods for details)

Table 5. Agreement between low-dose, non-contrast enhanced CT-attenuation correction study and CTA in 10 LVV patients

	PET/CT	CTA	*ICC (95% CI)
Diameter ascending aorta, mean (SD) mm	34.08 (6.10)	34.35 (6.07)	0.998(0.990-0.999)
Diameter descending thoracic aorta, mean (SD) mm	31.45 (8.86)	31.10 (8.92)	0.999(0.994-1.000)
Diameter suprarenal abdominal aorta, mean (SD) mm	29.08 (15.40)	28.72 (15.29)	0.999(0.998-1.000)
Diameter infrarenal abdominal aorta, mean (SD) mm	19.41 (6.53)	19.41 (6.38)	0.999(0.995-1.000)

*Intraclass correlation coefficients (ICC); p value <0.0001 for all aortic levels.

Figures

Figure 1. Evaluation of aortic diameters on PET/CT and CTA. Measurement of aortic diameters at the four defined levels on low-dose, non-contrast enhanced CT-attenuation correction study (A: ascending aorta; B descending thoracic aorta; C suprarenal abdominal aorta; D infrarenal abdominal aorta) and CTA (E: ascending aorta; F descending thoracic aorta; G suprarenal abdominal aorta; H infrarenal abdominal aorta)