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ORIGINAL ARTICLE

Risk of ischaemic events at giant cell arteritis diagnosis according to PET/CT findings

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Abstract

Purpose To analyse the risk of ischaemic events in patients with newly diagnosed giant cell arteritis (GCA) according to PET/CT findings.

Methods PET/CT was performed during the first 10 days of steroid therapy. Clinical manifestations at diagnosis, and physical examination and PET/CT findings were recorded and compared according to the presence or absence of ischaemic symptoms at disease onset. Analysed territories included the ascending aorta, aortic arch, descending aorta, abdominal aorta, carotid arteries, brachiocephalic trunk, vertebral arteries, subclavian arteries and axillary arteries.

Results The study group comprised 30 patients with a median age of 80.8 years. Of these patients, 21 (70%) reported ischaemic symptoms at diagnosis, and 13 (43.3%) had permanent visual loss. Of the 30 patients, 77.8% showed large vessel vasculitis (including aortic and vertebral artery involvement) on PET/CT, and 60% had isolated involvement of the vertebral territory. Vertebral arteries were more frequently involved in patients with ischaemic symptoms (OR 5.0, 95% CI 0.99–24.86, $p = 0.051$). The presence of vertebral artery involvement in the absence of aortic involvement was associated with the presence of ischaemic manifestations (Fisher's exact test, $p = 0.001$). The presence of aortitis was found to protect against the development of permanent visual loss (OR 19.0, 95% CI 2.79–127.97, $p = 0.001$).

Conclusion Our findings suggest an association between the vascular pattern on PET/CT at the time of GCA diagnosis and the risk of ischaemic events.

Keywords Vasculitis · Temporal arteritis · Giant cell arteritis · Inflammation · Radionuclide imaging

Introduction

Giant cell arteritis (GCA) is the most frequently diagnosed vasculitis among patients older than 50 years [1, 2]. The pathogenesis of the disease is poorly understood but epidemiological data suggest that ageing plays a central role in the genetically susceptible population. Involvement of the temporal arteries is typical, but other arterial territories (including the aorta) are frequently affected [3]. Vascular remodelling secondary to inflammation leads to vessel stenosis and occlusion [4]. There are no specific clinical symptoms that lead to the diagnosis of GCA, but headache and ischaemic symptoms such as jaw claudication and transient visual loss or permanent visual loss (PVL) may raise suspicion. PVL is mainly due to anterior ischaemic optic neuropathy (AION). It is associated with poorer functional outcomes and is one of the most feared events in GCA. AION and stroke are the most frequent ischaemic events related to GCA [5]. Abnormalities of the temporal arteries on physical examination (decrease or absence of pulse, and tenderness or enlargement of the artery) are typical signs. An increase in acute-phase reactants is typical [6]. Temporal artery biopsy (TAB) is the gold standard for

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GCA diagnosis, but a normal result does not rule out the disease.

Classification of GCA is based on the 1990 American College of Rheumatology (ACR) criteria, that have a sensitivity of 95.3% and a specificity of 90.7% [7]. The ACR criteria consider clinical signs and symptoms suggestive of temporal artery involvement along with a raised erythrocyte sedimentation rate (ESR) and a positive TAB, but extratemporal vessel involvement is not considered to confirm or rule out the diagnosis. This can lead to false-negative diagnosis, because GCA without cranial symptoms is possible [8].

Vascular involvement in GCA has been extensively studied by imaging techniques. Doppler ultrasonography (DUS) of the temporal arteries has a good positive predictive value in patients with suspected GCA [9]. Studies of extracranial vascular territories with DUS have shown involvement of the axillary, brachial and iliac arteries in some patients. These territories are more frequently involved in patients with aortitis [10]. ^{18}F-FDG PET/CT has a good diagnostic accuracy for GCA with a pooled sensitivity and specificity of 83.3% and 89.6%, respectively [11]. This technique is useful for the detection of large vessel vasculitis (LVV) [12], a condition that has been associated with an increased risk of the development of aortic complications within 5 years of diagnosis, including aneurysm and aortic dissection [13]. Muratore et al. [14] found that patients with involvement of the large vessels have a lower rate of vision loss but a higher relapse rate, and also need higher corticosteroid doses.

To date, few studies evaluating PET/CT findings according to the clinical signs and symptoms present at disease onset have been published. The study of this field is critical, since it may have therapeutic and prognostic implications in daily clinical practice. The objective of the present study was to evaluate the existence of different patterns of vascular involvement on PET/CT in patients with GCA according to the presence or absence of ischaemic manifestations at disease onset.

Materials and methods

Patients

All patients diagnosed with GCA between January 2013 and January 2017 at the Hospital Vall d'Hebron, a tertiary referral centre in Barcelona, Spain, were assessed for potential participation in the study. Newly diagnosed patients who met the 1990 criteria and who had had a PET/CT scan performed during the first 10 days of corticosteroid treatment were included [15–17]. The study was approved by the Ethics Committee of our institution.

Patients were prospectively enrolled and empirically treated with corticosteroids. All patients underwent a clinical evaluation, which included medical history review and physical examination. TAB was performed in all patients as part of the diagnostic algorithm. Steroids were started in all patients at the time of clinical diagnosis. Patients with ocular symptoms received high doses of steroids (500–1,000 mg/day for 3 days) followed by oral prednisone 1 mg/kg/day (up to a maximum dose of 60 mg/day). Patients without ocular symptoms were started on oral prednisone 1 mg/kg/day (maximum dose of 60 mg/day). Delay in diagnosis was calculated as the period between appearance of the first symptom and diagnosis. No patients were under methotrexate or tocilizumab treatment at inclusion.

Two different clinical subgroups were considered according to the presence or absence of ischaemic manifestations at disease onset. These manifestations included ocular symptoms (transient visual loss, PVL or diplopia), jaw claudication and cerebrovascular events. Jaw claudication was considered an ischaemic symptom according to previous studies indicating that this manifestation has an ischaemic origin [5]. Clinical variables comprised age at diagnosis, sex, duration of symptoms prior to diagnosis, history of hypertension, diabetes mellitus or dyslipidaemia, and clinical signs and symptoms of GCA at the time of disease diagnosis. TAB was performed in all patients to confirm GCA and was considered positive if an inflammatory infiltrate along with disruption of the elastic lamina were present. The presence of giant cells was not mandatory to classify a specimen as positive. Laboratory data comprised ESR, fibrinogen levels and platelet counts. Colour DUS was performed in all patients to determine the presence of the halo sign.

PET/CT examination

Patients were required to fast for a minimum of 6 h prior to intravenous administration of 3.7 MBq/kg (222–370 MBq) of ^{18}F-fluorodeoxyglucose (^{18}F-FDG). Glucose levels below 140 mg/dL were required in all patients prior to administration of the radiopharmaceutical. Before scanning, the patients rested for a minimum of 60 min.

Images were obtained using a Siemens Biograph mCT, which combines a spiral 64-slice CT scanner (210 keV, 120 mAs; CARE Dose) and a dedicated PET scanner, from the skull to the upper third of both femurs. Images were acquired 60 min after administration of the radiopharmaceutical. Delayed images were obtained at 120 min when nonvascular territories adjacent to the evaluated arteries showed significant hypermetabolism that could lead to misinterpretation of the results. The images generated were interpreted by nuclear medicine specialists on a *syngo*.-via workstation (Siemens Healthcare). Radiologists evaluated the extravascular findings using OsiriX MD software on a Mac as part of clinical practice in our centre.

The PET/CT images were evaluated by two nuclear medicine specialists blinded to the clinical information regarding the presence of ocular and/or ischaemic symptoms. Interpretation of the studies and final diagnosis regarding positive or negative vascular inflammation included visual and semiquantitative analysis.

Table 1 Clinical, laboratory and imaging findings of the entire cohort and subgroups of patients with and without ischaemic symptoms

Variable	Entire cohort	Ischaemic symptoms		
		No	Yes	*p* value
Number (%) of patients	30	9 (30%)	21 70%)	
Diagnostic delay (weeks). median (IQR)	4 (2.0–14.0)	12 (8.0–18.0)	4 (2.0–12.0)	0.03
Age at diagnosis (years), median (IQR)	80.8 (72.7–84.4)	72.4 (63.1–76.2)	83.8 (80.0–85.5)	0.001
Female gender	70.0%	6 (66.7%)	15 (71.4%)	1.00
Headache	73.3%	4 (44.4%)	18 (85.7%)	0.03
Scalp tenderness	36.7%	2 (22.2%)	9 (42.9%)	0.42
Polymyalgia rheumatica	26.7%	3 (33.3%)	5 (23.8%)	0.67
Fever	13.3%	2 (22.2%)	2 (9.5%)	0.56
Constitutional syndrome	36.7%	6 (66.7%)	5 (23.8%)	0.04
Temporal artery enlargement	61.1%	5 (55.6%)	13 (65.0%)	0.69
Absence of temporal artery pulse	82.8%	5 (55.6%)	19 (95.0%)	0.02
Hypertension	43.3%	1 (11.1%)	12 (57.1%)	0.04
Dyslipidaemia	43.3%	3 (33.3%)	10 (47.6%)	0.69
Diabetes mellitus	16.7%	1 (11.1%)	4 (19.0%)	1.00
Anaemia	76.7%	8 (88.9%)	15 (71.4%)	0.39
ESR (mm/h), mean (SD)	95.34 (28.3)	97.4 (36.7)	94.4 (24.7)	0.79
Platelets ($\times 10^6$/L), mean (SD)	374,000 (305,000–471,000)	425,625 (114,217.8)	372,804.8 (120,445.1)	0.29
Fibrinogen (g/L), mean (SD)	5.4 (4.2–6.3)	5.8 (1.23)	5.1 (1.04)	0.17
Positive temporal artery biopsy	26 (89.30%)	7 (88.90%)	18 (100.0%)	0.10
Halo sign on Doppler ultrasonography	46.2%)	1 (12.5%)	11 (61.1%)	0.04
Delay in PET/CT (days), median (IQR)	5.0 (2.0–7.0)	2 (0.0–7.0)	5 (2.0–6.0)	0.38
Involvement on PET/CT				
Globally positive	76.7%	7 (77.8%)	16 (76.2%)	1.00
Supraaortic trunk	66.7%	5 (55.6%)	15 (71.4%)	0.43
Vertebral arteries	60.0%	3 (33.3%)	15 (71.4%)	0.1
Carotid arteries	16.7%	5 (55.6%)	0 (0.0%)	0.001
Brachiocephalic trunk	23.3%	5 (55.6%)	2 (9.5%)	0.014
Intrathoracic LVV	26.7%	7 (77.8%)	2 (9.5%)	0.001
Aortitis	26.7%	6 (66.7%)	2 (9.5%)	0.003
Subclavian arteries	30.0%	7 (77.8%)	2 (9.5%)	0.001
Axillary arteries	30.0%	6 (66.7%)	3 (14.3%)	0.008
Ascending thoracic aorta	26.70%	6 (66.7%)	2 (9.5%)	0.003
Descending thoracic aorta	26.70%	6 (66.7%)	2 (9.5%)	0.003
Abdominal aorta	20.0%	5 (55.6%)	1 (4.8%)	0.005

ESR erythrocyte sedimentation rate, *IQR* interquartile range, *LVV* large vessel vasculitis, *SD* standard deviation

For the visual analysis, a four-point visual scale was used based on the FDG uptake in the vascular wall of each territory compared to the liver uptake as the reference, with the following categories: *grade 1* vascular wall uptake lower than liver uptake, *grade 2* vascular wall uptake equal to liver uptake, *grade 3* vascular wall uptake higher than liver uptake, and *grade 0* vascular wall uptake similar to the mediastinal blood pool. Positivity was defined as grade 3.

All the reports included information on the ascending aorta, aortic arch, descending aorta, abdominal aorta, carotid arteries, brachiocephalic trunk (BCT), vertebral arteries, subclavian arteries and axillary arteries [17]. Hypermetabolism in one or more territories was considered to indicate the presence of LVV [18]. Intrathoracic LVV was considered to be present if the aortic and/or subclavian arteries were involved. A PET/CT image was considered to be positive if one or more territories with grade 3 uptake were present.

Statistical analysis

Descriptive statistics were used to compare clinical groups according to the presence or absence of ischaemic symptoms.

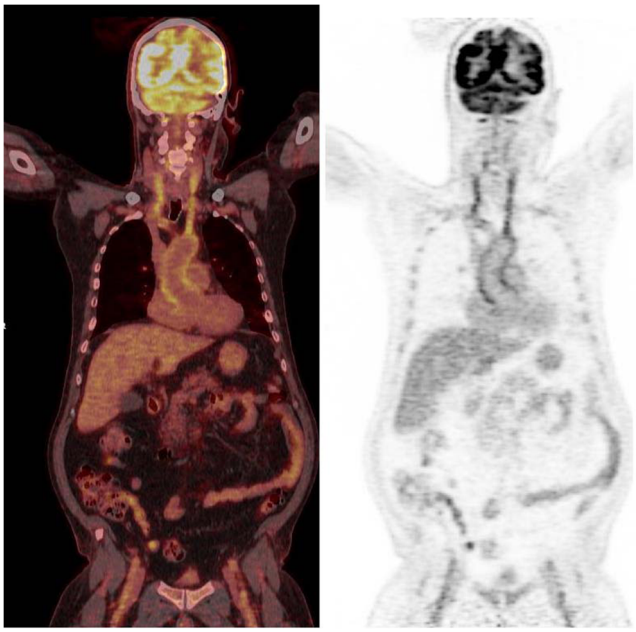

Fig. 1 Large vessel vasculitis in a patient with GCA

Data are expressed as numbers or proportions. Continuous variables are expressed as mean (standard deviation) or median (interquartile range), as appropriate. Groups were compared using a *t*-test or the Wilcoxon rank-sum test, according to the variable distribution. Categorical data were evaluated using the chi-squared test or Fisher's exact test (if the cell value was <5). Patients with missing data were excluded from the analysis. Odds ratios (OR) and 95% confidence intervals (CI) were calculated. A p value <0.05 was considered statistically significant. The analysis was performed using Stata 14.2 (College Station, TX, USA).

Results

The study group comprised 30 patients, 21 (70%) women, with a median age at diagnosis of 80.8 years (range 72.7–84.4 years). Overall, 21 patients (70.0%) reported ischaemic manifestations, and 13 patients (43.3%) had PVL. Four patients had jaw claudication only. One patient had cerebrovascular involvement, which was preceded by transient visual loss. Raynaud's phenomenon and limb ischaemic claudication was not present in any patient. Table 1 summarizes the demographic, clinical and imaging results in the entire cohort, and in relation to the presence or absence of ischaemic events.

Patients with ischaemic manifestations were older (p = 0.001), and more frequently had headache (p = 0.03), absent temporal artery pulse on physical examination (p = 0.02) and the halo sign (p = 0.04). In contrast, patients with ischaemic manifestations less frequently had constitutional symptoms (p = 0.04). Diagnosis delay was shorter in patients with ischaemic manifestations (p = 0.03). Both groups showed similar TAB positivity (p = 0.10). In four patients, TAB was not evaluated due to the poor quality of the specimen. The results are summarized in Table 1. The results were similar when only patients with PVL were analysed.

PET/CT

PET/CT was performed with a similar delay after the start of corticosteroid therapy with no significant difference between the groups. The results are shown in Table 1. Globally, PET/CT was positive in at least one vascular territory in 76.7% of patients (Fig. 1). No significant difference in the percentage of patients with a positive PET/CT scan was found between those with an without ischaemic manifestations. Patients with ischaemic manifestations showed vertebral artery hypermetabolism on PET/CT more frequently than patients without, although the difference did not reach statistical significance (71.4% vs. 33.3%, OR 5.0 (0.99–24.86), p = 0.051; Fig. 2). In this subset of patients, the remaining vascular territories (including carotid arteries, BCT, subclavian arteries, axillary arteries and aorta) were less frequently involved. The ORs for the involved territories on PET/CT are shown in Table 2.

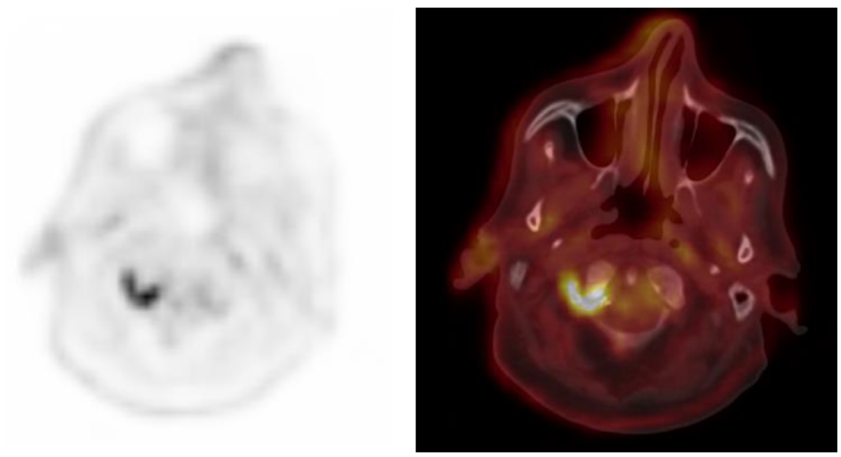

Fig. 2 Vertebral artery involvement in a patient with GCA with ischaemic symptoms

Table 2 Odds ratios for ischaemic manifestations in relation to involved arterial territories on PET/CT

Arterial territory involvement	Ischaemic manifestations		
	Odds ratio	95% confidence interval	*p* value
Vertebral arteries	5.0	0.99–24.86	0.051
Subclavian arteries	0.03	0.004–0.23	<0.001
Brachiocephalic trunk	0.08	0.01–0.54	0.006
Carotid arteries	N/A		
Axillary arteries	0.08	0.01–0.49	0.004
Ascending thoracic aorta	0.05	0.008–0.36	0.001
Descending thoracic aorta	0.05	0.008–0.36	0.001
Abdominal aorta	N/A		
Intrathoracic LVV	0.03	0.004–0.23	<0.001
Aortitis	0.05	0.008–0.36	0.001

No patients had ischaemic manifestations and carotid artery hypermetabolism on PET/CT (*N/A*)

LVV large vessel vasculitis

Comparing patients with and without PVL, there were no significant differences in the proportions with vertebral artery involvement (61.5% vs. 58.8%, respectively; $p = 0.88$) and the proportions with BCT involvement (7.7% vs. 35.3%, respectively; $p = 0.1$). However, compared with patients without PVL, a lower proportion of patients with PVL showed carotid artery involvement on PET/CT (0.0% vs. 29.4%), although statistical significance was not reached ($p = 0.052$), and a lower proportion showed intrathoracic large vessel hypermetabolism (7.7% vs. 47.1%, $p = 0.042$). Indeed, the presence of intrathoracic LVV was found to protect against the development of PVL (OR 10.67, 95% CI 1.12–101.34, $p = 0 = 0.04$).

All patients with vertebral involvement but no aortic involvement showed ischaemic manifestations at disease onset. In contrast, none of the patients with aortic involvement but no vertebral hypermetabolism showed ischaemic symptoms (Table 3). Therefore, the presence of ischaemic symptoms was associated with distinct PET/CT findings related to vertebral and aortic involvement (Fisher's exact test, $p = 0.001$).

Table 3 Patients with aorta and/or vertebral artery hypermetabolism according to the presence of ischaemic manifestations

Ischaemic symptoms	Involvement on PET/CT			
	Aorta: No		Aorta: Yes	
	Vertebral arteries: No	Vertebral arteries: Yes	Vertebral arteries: No	Vertebral arteries: Yes
No	3	0	3	3
Yes	6	13	0	2

Discussion

GCA is a heterogeneous disease with two main different clinical subsets that may coexist [19]: local and systemic with predominantly vascular involvement (cranial vs. systemic GCA). In the present study we analysed the usefulness of PET/CT at the time of GCA diagnosis to distinguish between patients with and without ischaemic manifestations. Patients with intrathoracic LVV had a lower risk of developing PVL. Furthermore, all patients with vertebral involvement but no aortic hypermetabolism showed ischaemic manifestations. In contrast, none of the patients with aortic but no vertebral artery involvement showed ischaemic events. To our knowledge, this is the first study evaluating the risk of ischaemic manifestations according to PET/CT findings in patients with newly diagnosed GCA.

Previous studies have shown a higher maximum standardized uptake value (SUVmax) in different vascular territories (aorta, subclavian arteries, carotid arteries, axillary arteries, iliac arteries and femoral arteries) on PET/CT at the time of GCA diagnosis [20, 21]. In fact, aortitis has been reported in about 40% of patients with newly diagnosed GCA [22]. The global prevalence of aortic involvement in our cohort was slightly lower than found in previous studies [22, 23]. This was probably due to the high percentage of patients with visual symptoms included in the study. However, including all the different vascular territories, the proportion of patients with large vessel involvement was similar in our series to that found by others. Our patients with ischaemic manifestations had a lower prevalence of aortitis, in accordance with results reported by Muratore et al. [14]. However, the prevalence of intrathoracic large vessel involvement in our series was lower than previously reported [24]. However, analysing patients with and without ischaemic events separately, among those with ischaemic manifestations, the proportion with intrathoracic LVV was lower than previously reported, while among those without ischaemic manifestations, the proportion with LVV was similar to that found in other studies which considered GCA patients globally [22].

A trend towards aortitis protecting against ischaemic events (including ocular involvement) was observed (OR 19.0, 95% CI 2.79–127.97, $p = 0.001$). In contrast, vertebral artery involvement was higher in patients with ischaemic symptoms (OR 5.0, 95% CI 0.99–24.86, $p = 0.051$). Even though significant differences were not reached, our findings indicate that patients with vertebral artery involvement on PET/CT at the time of GCA diagnosis have a high risk of developing ischaemic manifestations. Previous studies have shown that a high proportion of patients with vertebral artery involvement have a history of stroke at the time of GCA diagnosis [24]. In our series, only one patient had a history of stroke at disease onset and showed vertebral involvement on PET/CT. Study of the supraaortic territories (carotid and vertebral arteries) in GCA

seems to be critical. It has been shown that the presence of hypermetabolism in these territories, considered as a ratio of vascular SUVmax to liver SUVmean of >1, yields the best area under the curve for GCA diagnosis (AUC 0.83) with a sensitivity of 71% and specificity of 91%. Bearing in mind these results and our findings, we consider that the vertebral arteries should be carefully studied in patients with suspected GCA, not only to support the diagnosis but also to assess the risk of development of ischaemic events [25].

In the present study, patients with ischaemic manifestations were older, more frequently had hypertension and an absent temporal pulse on physical examination than patients without, and less frequently had constitutional symptoms, in line with the findings of previous studies [26–29]. It is noteworthy that a higher proportion of patients with ischaemic symptoms showed the halo sign on DUS, in contrast to the findings of previous studies [30]. We believe that these findings reflect the predominant cranial vascular involvement in patients with ischaemic manifestations.

Our study had several limitations. The sample size was small, and the high proportion of patients with ocular involvement in our cohort, due to our clinical setting (a tertiary care hospital with an ophthalmological emergency department), may be a bias. Additionally, although PET/CT was performed during the first 10 days of steroid therapy in all patients, we cannot rule out the possibility that corticosteroid treatment might have influenced the low prevalence of aortitis that we found. In this context, Nielsen et al. [15] have recently shown that the detection of arterial wall inflammation may be suboptimal after 3 days of glucocorticoid therapy [15]. Therefore, we may have underestimated the prevalence of vascular involvement in some patients, but it is known that the different territories have similar responses to corticosteroid therapy [15]. Thus, the distribution of radiotracer and the proportion of patients with involvement of the different territories studied will be similarly affected by the treatment.

We believe that our findings may have therapeutic and prognostic implications in daily clinical practice. Future research is needed to establish the role of PET/CT in diagnosing GCA and assessing the risk of ischaemic events at disease onset. Finally, the inclusion of this technique in the GCA classification criteria should be considered.

In summary, our findings suggest that patients with vertebral artery involvement and no aortic hypermetabolism on PET/CT at the time of GCA diagnosis have a high risk of developing ischaemic events.

Compliance with Ethical Standards

Conflicts of interest None.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the principles of the 1964 Declaration of Helsinki and its later amendments or comparable ethical standards. The protocol was approved by the Ethics Committee of the Hospital Vall d'Hebron.

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