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Original Article

Diagnostic accuracy of ultrasound for detecting large-vessel giant cell arteritis using FDG PET/CT as the reference

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Abstract

Objectives. The diagnostic accuracy of axillary artery US in the diagnosis of large-vessel (LV)-GCA using ^{18}F-fluorodeoxyglucose (FDG) PET/CT as reference standard was prospectively evaluated in GCA-suspected patients. As an exploratory analysis, the diagnostic accuracy of cranial artery FDG PET/CT was evaluated.

Methods. Briefly, the inclusion criteria were age ≥50 years, raised inflammatory markers and potential GCA symptoms. Patients in immunosuppressive therapy or with a previous diagnosis of GCA or PMR were excluded. Examinations were performed pre-treatment. LV-GCA reference diagnosis was a clinical diagnosis of GCA and PET-proven LV inflammation. GCA patients fulfilling ACR criteria were considered as cranial-GCA (c-GCA). Patients without GCA were considered controls. Receiver operating characteristic curve analysis of the US-measured axillary intima-media thickness was performed. FDG uptake in temporal, maxillary and vertebral arteries was also assessed.

Results. Forty-six patients were diagnosed with LV-GCA, 10 with isolated c-GCA, and in 34 patients GCA was dismissed. Axillary US yielded a sensitivity of 76% and a specificity of 100% for LV-GCA. An axillary intima-media thickness cut-off of 1.0 mm yielded a sensitivity of 74% and a specificity of 92%. Adding LV US to temporal assessment increased sensitivity from 71% to 97% (all GCA patients). Cranial artery PET showed a diagnostic sensitivity of 78% and specificity of 100% for c-GCA.

Conclusion. Axillary artery US shows high accuracy for the LV-GCA diagnosis. Building upon the recent EULAR recommendations, we propose a diagnostic algorithm with US as the first-line confirmatory test, not only in c-GCA-suspected patients, but in all patients suspected of GCA.

Key words: giant cell arteritis, large vessel vasculitis, diagnostic imaging, ultrasound, FDG PET/CT

Rheumatology key messages

- Axillary artery US has an excellent diagnostic accuracy for detecting PET-proven large-vessel GCA.
- US can be used as first-line imaging test in all patients suspected of GCA.
- A high specificity of cranial artery PET/CT is confirmed in a cohort of GCA-suspected patients.

Introduction

GCA may affect the aorta and its main branches, referred to as large-vessel (LV)-GCA, and/or the extracranial cephalic arteries, referred to as cranial-GCA (c-GCA). LV-GCA diagnosis is often delayed [1–4] because patients usually present with general symptoms such as fever/inflammation of unknown origin and weight loss [5–7], and are less likely than c-GCA patients to have cranial symptoms [1, 2, 8–10]. Patients with LV-GCA often undergo extensive examination programs on suspicion of infection or malignancy before GCA diagnosis is established. Therefore, there is an unmet need for earlier diagnosis and treatment in these patients.

The EULAR recommendations for the use of imaging in large-vessel vasculitis in clinical practice suggest

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CLINICAL SCIENCE

diagnostic imaging in all GCA-suspected patients [11]. US is the recommended first-line imaging in patients suspected of c-GCA, but no specific priority is given for LV-GCA imaging. Studies comparing the diagnostic performance of imaging tests are sparse.

Mainly considering cranial symptoms and findings, the traditionally applied reference standards in GCA, such as the ACR criteria and the temporal artery biopsy (TAB), are less sensitive to diagnose LV-GCA [1, 2, 8, 9, 12]. Not surprisingly, in GCA cases not fulfilling ACR criteria, diagnosis is more often confirmed by imaging [12].

Moreover, the ACR criteria are meant for classification of vasculitis patients for clinical trials, whereas for diagnostic purposes the criteria have limited specificity [12].

A good agreement between US and ^{18}F-fluorodeoxyglucose (FDG) PET findings of vasculitis was demonstrated in smaller selected GCA cohorts [13–16]. While these studies indicate a promising role for US in LV-GCA diagnosis, it is noticeable that most US studies found LV involvement in 29–54% of GCA patients [1, 17–19] *vs* 80–90% by FDG PET/CT [20] using either a clinical diagnosis or ACR 1990 criteria as reference, indicating the superiority of PET/CT for diagnosing LV-GCA. Although US has an excellent resolution compared with PET/CT, the limited visibility by US of thoracic arteries adds to the potential superiority of PET for large-vessel examination. Nevertheless, availability, safety and low price make US an attractive first-line imaging test also in LV-GCA diagnosis.

The primary objective of the present study was to prospectively evaluate the performance of US assessment of carotid and axillary arteries in diagnosing PET-proven LV-GCA in glucocorticoid-naïve patients suspected of new-onset GCA.

Recently, we reported high diagnostic accuracy of conventional FDG PET/CT to detect cranial artery inflammation in a case–control study of GCA patients *vs* malignant melanoma controls [21]. Therefore, as an exploratory analysis, we compared the diagnostic performance of US and PET for cranial artery inflammation and for the overall GCA diagnosis in GCA-suspected patients. Finally, the added support for imaging priority in GCA diagnosis is summarized in an algorithm for diagnostic evaluation of GCA-suspected patients.

Methods

Study design and definitions

Study design

This was a prospective observational cohort study of glucocorticoid-naïve patients suspected of new-onset GCA. Diagnostic accuracy of the index tests was evaluated against pre-defined reference standards. Patients were prospectively included from October 2014 to June 2018.

Reference standard

LV-GCA cases were patients with a clinical diagnosis of GCA and verified LV inflammation (aorta and/or supra-aortic branches) by FDG PET/CT with or without concomitant fulfilment of ACR criteria for GCA (considered c-GCA).

c-GCA cases, for the exploratory analysis of the performance of US and PET in c-GCA, were patients with a clinical diagnosis of GCA and fulfilling the 1990 ACR criteria, with or without concomitant LV-GCA.

Controls were GCA-suspected patients with negative TAB, no LV inflammation on PET and in whom GCA diagnosis was clinically dismissed.

Participants

Patients suspected of GCA referred to the Department of Rheumatology, Aarhus University Hospital, Denmark (secondary and tertiary referral centre), were consecutively considered for inclusion. Patients were not considered for inclusion if steroid-naïvety was compromised because of unequivocal symptoms of c-GCA requiring acute glucocorticoid treatment unless FDG PET/CT had been carried out by the time of referral.

Inclusion criteria were age $\geq$50 years; CRP $>$15 mg/l or ESR $>$40 mm/h; and either (i) cranial symptoms, (ii) new-onset extremity claudication or (iii) protracted constitutional symptoms (weight loss $>$5 kg or fever $>$38°C for $>$3 weeks or (iv) bilateral shoulder pain and morning stiffness. Exclusion criteria have been published for a subcohort [22], but briefly were: ongoing or recent glucocorticoid or other immunosuppressive treatment; previous diagnosis of GCA or PMR; and LV inflammation mimicking LV-GCA caused by other diseases, including autoimmune and infectious diseases with possible aortitis and other large-vessel disease.

The study was approved by The Central Denmark Region Committees on Health Research Ethics (reference number 1-10-72-246-16, 1-10-72-60-14 and 1-10-72-240-15) and The Danish Data Protection Agency (reference number 1-16-02-380-14 and 1-16-02-481-16), and was conducted in accordance with the principles of the Declaration of Helsinki. All patients gave their written informed consent.

Evaluations according to reference standard and index test

Clinical evaluation and diagnosis

An experienced rheumatologist performed a pre-treatment clinical evaluation to confirm eligibility criteria and establish the clinical diagnosis. The evaluation included history taking, physical examination, extensive laboratory screening (previously published [22]), the FDG PET/CT report and TAB. US was not considered for establishing the clinical diagnosis. Regarding vessel FDG uptake, the initial PET report, available to the clinician establishing the diagnosis, described the routine evaluation of large-vessel FDG uptake, considering uptake intensity higher than liver uptake consistent with large-vessel vasculitis, but did not include cranial arteries that were not evaluated by the time of inclusion.

All patients were referred for a TAB, which was considered positive in the presence of an inflammatory infiltrate

in any vessel wall layer. A clinical GCA diagnosis could be dismissed, even in patients fulfilling ACR criteria, if another more reasonable diagnosis was established.

FDG PET/CT

PET/CT scans were performed using a combined PET/CT scanner (either GE Discovery 690, GE Healthcare, Chicago, IL, USA; or Siemens Biograph 64 PET/CT, Siemens Healthcare, Erlangen, Germany). Institutional protocol, image acquisition and reconstruction parameters adhere to international guidelines and have been described previously [20–23]. In a few cases, FDG PET/CT was performed at other hospitals before referral to our department.

After enrolment, all PET images were assessed *en bloc* by an expert nuclear medicine physician (L.C.G.) blinded to clinical symptoms and findings. FDG uptake in the wall of LVs (ascending, descending and abdominal aorta, aortic arch, subclavian/axillary, carotid and ileo-femoral arteries), was graded on a 4-point scale as previously reported [22]. Homogeneous, segmental FDG uptake in the aorta and/or supra-aortic LVs (e.g. carotid, subclavian/axillary) above liver uptake (grade 3) was considered consistent with LV-GCA [20, 24, 25] (Fig. 1, lower panel). Cranial vessels (vertebral, maxillary and temporal arteries) were dichotomously scored and FDG uptake above surrounding tissue was considered consistent with cranial artery inflammation [21] (Fig. 1 upper panel). Interrater reliability for the assessment of large and cranial vessels was recently published [21, 22].

Index test, vascular US

US was performed prior to glucocorticoid treatment by one of four experienced [26] vascular sonographers (P.T., I.T.H., K.K.K. and B.D.N.), who were blinded to the PET scan.

HI VISION Avius (Hitachi Medical Systems Europe, Steinhausen, Switzerland) with a 5–18 MHz linear probe (EUP-L75) was used for all examinations. The common superficial temporal artery, its parietal and frontal branches (Fig. 1, cranial arteries, upper panel), and the common carotid and axillary arteries (Fig. 1, LV, lower panel) were evaluated on both sides. The carotid and axillary arteries were chosen for LV assessment since they are predilected vessels of inflammation in GCA and are easily accessible for US evaluation [1, 3, 16, 19, 27–29].

For the temporal artery US examination, high-definition dynamic harmonic imaging high resolution mode was applied, and the settings were: B mode gain, 20 dB; pulse repetition frequency, 2.5 kHz; colour gain, 30 dB. For carotid and axillary artery assessment, high-definition dynamic harmonic imaging deep scan mode was applied and the US settings were: B mode gain, 12 dB; pulse repetition frequency, 3.5 kHz; colour gain, 35 dB. For both examinations, focus point position was just below the region of interest; dynamic range was 70 dB and colour Doppler frequency, 6.5 MHz.

For each artery assessed, the presence or absence of a halo sign was evaluated. A halo was defined as a homogeneous, smooth, segmental, hypoechoic wall swelling well delineated towards the lumen (Fig. 1, left side). Inhomogeneous, irregular and patchy hyperechoic wall thickening and isolated wall thickening within 0.5 cm of bifurcations were not considered a halo. Positive findings were confirmed in transverse view. Compression sign could be evaluated to ensure true positivity (temporal arteries). The definitions applied are in concordance with recently published OMERACT definitions [30]. Measurement of the intima-media thickness (IMT) was performed in the systolic phase, on the lower wall in a longitudinal scan [31].

Interrater reliability among sonographers was evaluated for c-GCA and LV-GCA separately. The assessment comprised a static image and a video clip of a representative cranial and a representative LV artery from each study participant ($n = 79$).

Statistics

REDCap (Research Electronic Data Capture) tools hosted at Aarhus University was used for data collection and management [32]. Statistical analysis was performed using Stata (StataCorp 2015, Stata Statistical Software: Release 14; StataCorp LP, College Station, TX, USA).

Student's *t*-test or Mann–Whitney *U* test were used for quantitative data where applicable. Normality was checked using histograms and QQ-plot. Dichotomous data were evaluated by Fischer's exact test. Interreader agreement was evaluated by Fleiss kappa. Receiver operating characteristic (ROC) curve analysis was performed to estimate LV IMT cut-offs.

A significance level of 0.05 was considered statistically significant.

Results

Baseline characteristics of LV-GCA, isolated c-GCA and controls

A total of 102 patients were screened for eligibility. A patient flow diagram is shown in Fig. 2. Fifty-six patients were diagnosed with GCA, of whom 46 had LV-GCA. The clinical diagnosis of GCA was confirmed at a 6-month follow-up visit in 51/56 patients. Five patients were lost to follow-up, all of whom were TAB positive. Patients diagnosed with PMR were seen for follow-up after 1–2 months. They all responded well to moderate-dose prednisolone. For all other control patients, either an alternative diagnosis was confirmed, or patients recovered spontaneously and were followed until symptoms and finding were normalized.

Of the 102 patients screened, 4 patients who were excluded (2 with low CRP/ESR, 1 who withdrew consent, and 1 requiring glucocorticoid treatment before PET) had a final diagnosis of GCA.

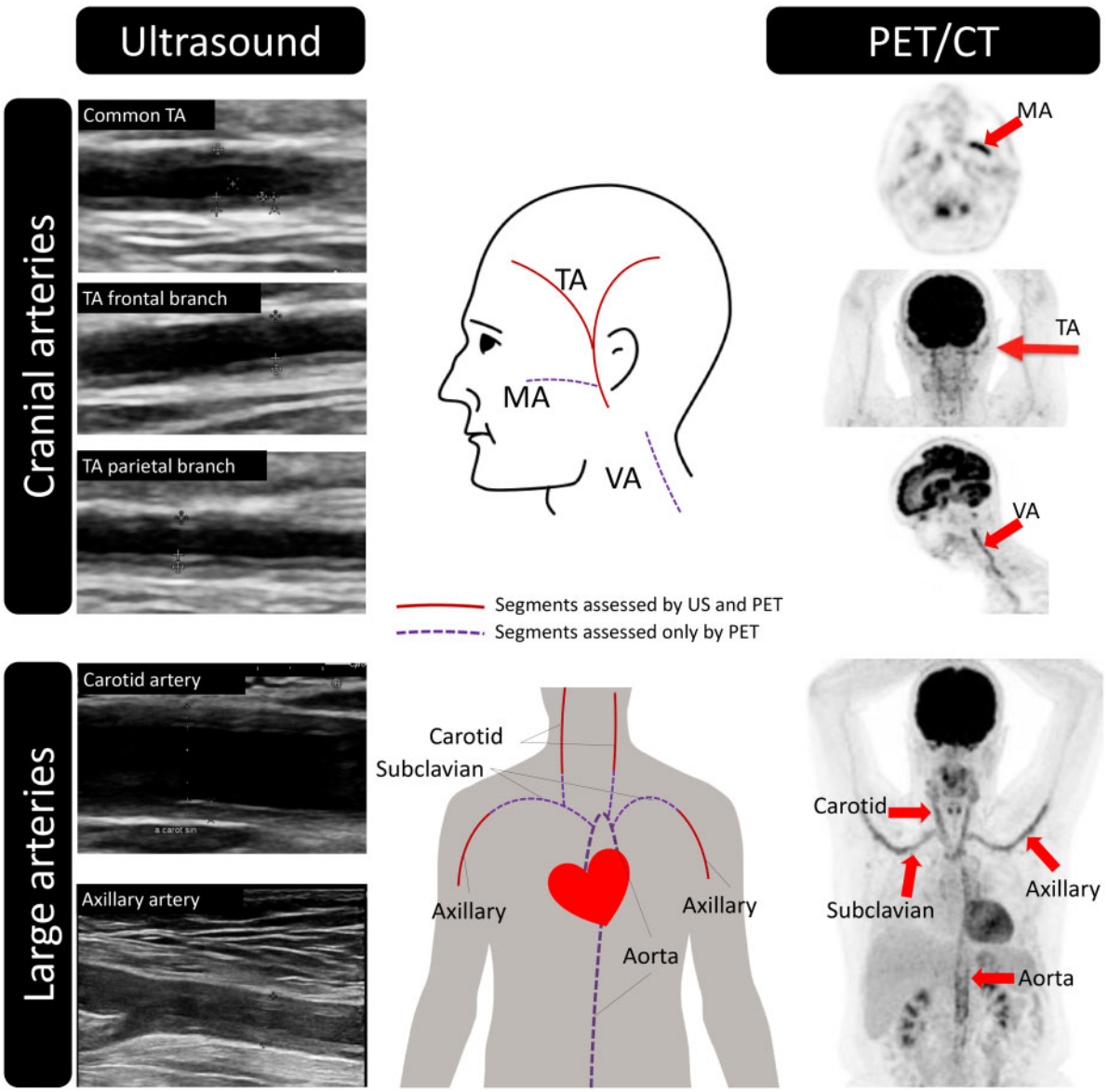
Baseline characteristics of LV-GCA cases and controls are shown in Table 1. Baseline characteristics of c-GCA patients and different subsets of controls can be

found in supplementary Table S1, available at *Rheumatology* online. In five GCA patients TAB was unsuccessful (procedure cancelled by surgeon $n = 1$, procedure cancelled by patient $n = 1$, biopsy specimen not including artery segment $n = 3$). TAB was performed in 25 of the 34 controls. The TAB procedure was called off in seven control patients in whom another diagnosis was established ruling out the suspicion of GCA, and in two PMR patients by study definition suspected of possible GCA, who opposed to having a TAB after the performance of imaging tests and the experience of a positive effect of initial glucocorticoid treatment.

Diagnostic sensitivity and specificity of vascular US in LV-GCA

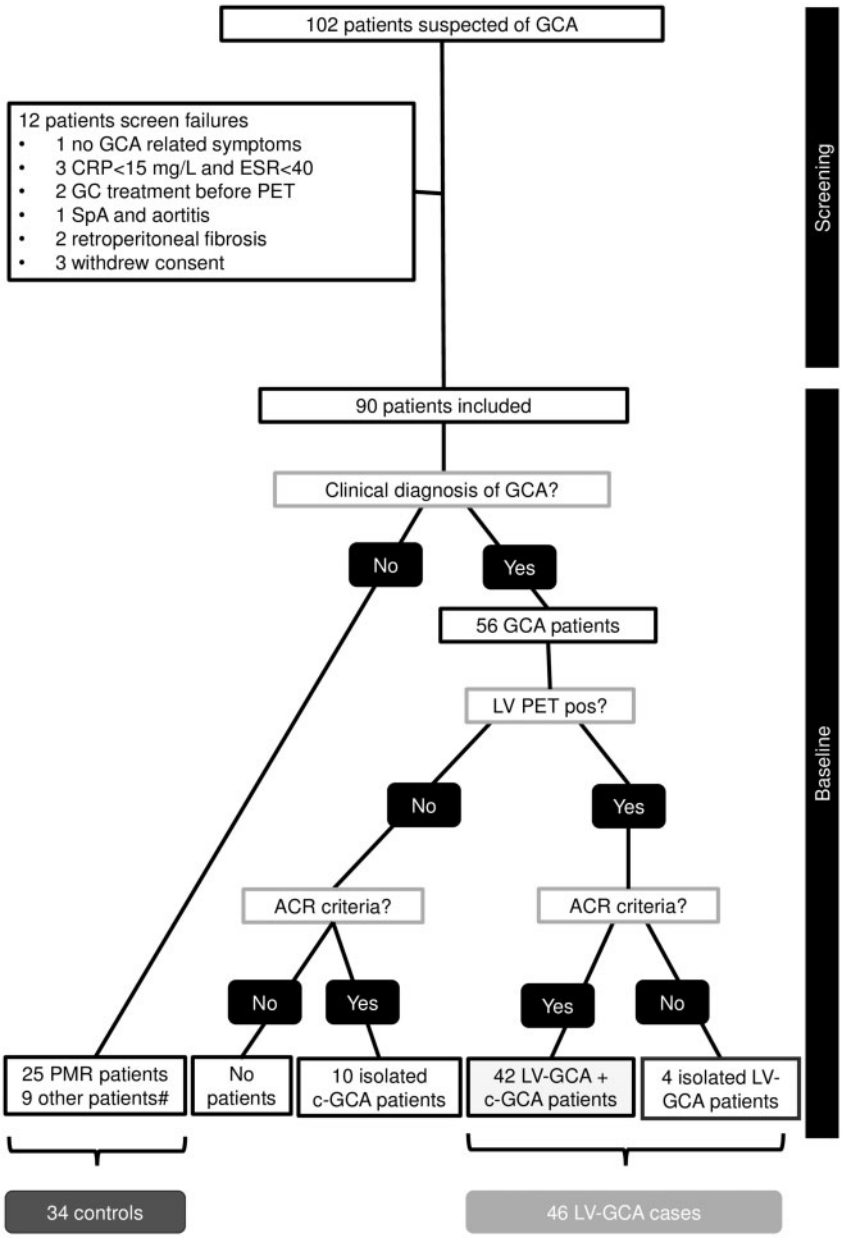
According to the pre-defined reference standards, the results of the US examination of all arteries (LVs and

Fig. 1 Assessment of cranial and LVs by US and FDG PET/CT



Upper panel: temporal artery US-positive defined as halo in common superficial temporal artery, frontal or parietal branch of the temporal artery. Cranial PET-positive defined as FDG uptake above surrounding tissue in vertebral, maxillary and/or temporal arteries. Lower panel: LV US-positive defined as US halo in axillary and/or carotid artery. LV PET-positive defined as vessel FDG uptake higher than liver FDG uptake in aorta and/or subclavian/axillary or carotid artery with or without involvement of other large arteries. LV: large vessel; FDG: ^{18}F-fluorodeoxyglucose; TA: temporal artery; MA: maxillary artery; VA: vertebral artery.

Fig. 2 Patient flow diagram



Patient flow chart showing screening, eligibility, inclusion of patients and final categorization of patients into LV-GCA, isolated c-GCA and controls. LV-GCA, patients with a clinical diagnosis of GCA and verified LV inflammation by FDG PET/CT with or without concomitant c-GCA; c-GCA, clinical diagnosis of GCA and fulfilling the 1990 ACR criteria; controls, GCA-suspected patients in whom GCA diagnosis was dismissed. The baseline evaluations are illustrated to show the categorization of patients and do not necessarily reflect the order of assessments. #Other diagnoses were infections or unspecific transient diseases. FDG: ^{18}F-fluorodeoxyglucose; TAB: temporal artery biopsy; c-GCA: cranial-GCA; LV-GCA: large-vessel GCA.

temporals), only LVs or only temporal arteries, in the diagnosis of GCA in general, LV-GCA and c-GCA, respectively, are shown in Table 2A–C.

A total of 36/46 LV-GCA patients were LV US positive, whereas all control patients were LV US negative, yielding a diagnostic sensitivity of 78% and a specificity of 100% (Table 2B). Interestingly, excluding carotid artery assessment from LV US examination only decreased sensitivity from 78% to 76%. Considering all GCA patients, US assessment of temporal and LV arteries showed a sensitivity of 91% and a specificity of 97% (Table 2A), compared with a sensitivity of only 71% and

Table 1 Baseline characteristics of LV-GCA cases and controls

	LV-GCA	Controls	*P*-value
Total number of patients	46	34	
Demographics			
Women, *n* (%)	28 (61)	16 (27)	0.26
Age, years (mean, range)	67 (51–84)	68 (51–84)	0.46
TAB and ACR fulfilment			
TAB positive/performed	31/41 (76)	0/25 (0)	<0.001
Fulfilment of 1990 ACR criteria for GCA	42 (91)	13 (38)	<0.001
Symptoms			
Headache	30 (65)	10 (29)	<0.01
Scalp tenderness or dysesthesia	12 (26)	4 (12)	0.07
Visual disturbances	10 (22)	3 (9)	0.14
Permanent loss of vision	0 (0)	0 (0)	
Amaurosis fugax	3 (7)	0 (0)	0.26
Double vision	1 (2)	1 (3)	1
Blurred vision	7 (15)	2 (15)	0.29
Jaw claudication	9 (20)	0 (0)	<0.01
Myalgia	22 (48)	31 (91)	<0.001
Cough	22 (48)	6 (18)	0.01
New limb claudication	10 (22)	2 (6)	0.06
Morning stiffness	10 (22)	22 (65)	<0.001
Severe constitutional symptoms[a]	40 (87)	20 (59)	<0.01
Fever	26 (56)	14 (41)	0.26
Weight loss	40 (87)	15 (44)	<0.001
Weight loss (if any), mean (S.D.), kg	4.3 (1.9)	4.1 (2.0)	0.79
Symptom duration, weeks (median, range)	13 (2–72)	6.5 (2–36)	<0.001
Patient-reported outcomes			
Pain NRS, median (IQR)	4 (2–7)	8 (5–9)	<0.001
Global NRS, median (IQR)	8 (5–10)	6.5 (5–8)	0.45
Inflammatory markers			
CRP mg/l, median (95% CI)	71 (59–85)	48 (37–62)	<0.05
Albumin g/l, mean (95% CI)	31 (30–32)	33 (32–35)	<0.01
Haemoglobin, mmol/l, mean (95% CI)	6.7 (6.5–6.9)	7.7 (7.4–8.0)	<0.001
Platelets $\times 10^9$/l, mean (95% CI)	452 (412–492)	441 (395–489)	0.74
FDG PET/CT characteristics			
LV PET positive (by reference definition)	46 (100)	0	
Number of PET-positive LV segments[b], median (S.D.)	8 (3)	0	
Aortitis	42 (91)	0	
Subclavian/axillary artery positive	38 (82)	0	
Carotid artery positive	22 (48)	0	
Femoral artery positive	22 (48)	0	
Cranial artery PET positive	37 (80)	0	

Patients with isolated c-GCA are not shown in this table. If not otherwise specified, data are numbers and percentages (%) of patients.
[a]Weight loss ≥5 kg, fever ≥38 °C or profound night sweats.
[b]Ten large vessel segments were assessed. LV-GCA: large-vessel GCA; NRS: numerical range scale; IQR: interquartile range; c-GCA: cranial-GCA; LV: large vessel; TAB: temporal artery biopsy; FDG: ^{18}F-fluorodeoxyglucose.

a specificity of 97% if only temporal arteries were assessed (not shown for the entire GCA cohort). The accuracy of US for the LV-GCA and c-GCA subgroups are shown in supplementary Table S2, available at *Rheumatology* online.

In all patients with PET-positive findings in the axillary artery, the positive FDG uptake was seen on both sides, whereas patients with positive US findings in axillary arteries sometimes were unilateral. Consequently, axillary US using PET as a reference, on a segment level, revealed a slight reduction in sensitivity from 78% to 73% (Table 3A). For the carotid artery, sensitivity of the halo sign was only 14%, but the specificity was 100% (Table 3B). Interestingly, two c-GCA patients had LV artery halos on US (one carotid and one axillary) although they were LV PET negative.

The mean IMT in PET positive axillary arteries was 1.32 mm as compared with 0.64 mm in PET-negative axillary arteries ($P < 0.0001$). An area under the curve of

Table 2 FDG PET/CT and US diagnostic performance in different vascular domains using predefined reference standard diagnosis

Ultrasound					
(A) US of temporal and large arteries in overall GCA diagnosis					
	All GCA (LV-GCA + c-GCA)	Controls		Sensitivity	91% (80–97)
LV or TA US pos	51	1		Specificity	97% (85–100)
LV and TA US neg	5	33		LR+	31
				LR–	0.1
Total	56	34			
(B) US of large arteries in LV-GCA diagnosis					
	LV-GCA (± c-GCA)	Controls	Isolated c-GCA (without LV-GCA)	Sensitivity	78% (64–89)
LV US pos	36	0	2	Specificity	100% (89–100)
LV US neg	10	34	8	LR+	∞
				LR–	0.2
Total	46	34	10		
(C) US of temporal arteries in c-GCA diagnosis					
	c-GCA (ACR ± LV-GCA)	Controls	Isolated LV-GCA (not ACR criteria)	Sensitivity	73% (59–84)
TA US pos	38	1	2	Specificity	97% (85–100)
TA US neg	14	33	2	LR+	25
				LR–	0.3
Total	52	34	4		
FDG PET/CT					
(D) PET of cranial arteries in c-GCA diagnosis					
	c-GCA (ACR ± LV-GCA)	Controls	Isolated LV-GCA (not ACR)	Sensitivity	79% (65–89)
Cranial PET pos	41	0	2	Specificity	100% (90–100)
Cranial PET neg	11	34	2	LR+	∞
				LR–	0.2
Total	52	34	4		

LV-GCA: LV PET positive; c-GCA: fulfilling ACR criteria. LV PET positive: FDG uptake (>liver uptake) in aorta and/or subclavian/axillary or carotid artery ± involvement of other LVs. Positive uptake confined to cranial arteries was not considered LV-GCA. Cranial PET positive: FDG uptake in vertebral, maxillary and/or temporal arteries. LV US positive: US halo in axillary and/or carotid artery. TA US positive: halo in common superficial temporal artery, frontal or parietal branch of the temporal artery. Controls: GCA diagnosis dismissed. LV: large vessel; TA: temporal artery; US: ultrasound; c-GCA: cranial-GCA; LR: likelihood ratio; FDG: ^{18}F-fluorodeoxyglucose; pos: positive; neg: negative.

0.87 (95% CI: 0.76, 0.90) was obtained by ROC curve analysis of axillary IMT with axillary PET diagnosis as a reference. An IMT cut-off value of 1.0 mm revealed a sensitivity of 70% and a specificity of 93% (supplementary Table S3, available at *Rheumatology* online).

In contrast, IMT in carotid arteries was not significantly different in PET-positive and PET-negative segments (0.72 *vs* 0.80 mm, $P = 0.12$). ROC curve analysis of carotid artery IMT revealed an area under the curve of 0.54, and a sensitivity of 16% and a specificity of 98% with a 1.1 mm IMT cut-off (supplementary Table S3, available *Rheumatology* at online).

A positive LV halo sign was found in 34/42 (81%) of patients with PET-proven aortitis. Four of 14 patients without PET-proven aortitis had a positive LV halo.

Interrater reliability of US assessment

Evaluating interrater reliability for the interpretation of the halo sign showed an agreement of 95% (95% CI: 92, 99) and 94% (95% CI: 89, 98), and a Fleiss kappa of 90% (95% CI: 83, 97) and 87% (95% CI: 79, 95) for LV and temporal arteries, respectively.

Diagnostic accuracy of FDG PET/CT of cranial and LV arteries in GCA

PET confirmation of the c-GCA diagnosis by cranial artery assessment showed excellent diagnostic accuracy (Table 2D). The accuracy of PET for the LV-GCA diagnosis was not evaluated since PET is the reference for LV-GCA in this study. A total of 53/56 patients with a clinical diagnosis of GCA were PET positive (LV and/or cranial).

Comparing US *vs* PET in vessel segments and overall GCA diagnosis

Bearing in mind the reservation that the clinical diagnosis was established with knowledge of the PET scan regarding LV inflammation, we report the ability of PET *vs* US to confirm GCA in Table 3. Concerning c-GCA,

Table 3 Comparing US and PET in vessel segments and for diagnosis of GCA and c-GCA

Artery segment level						
(A) Axillary artery						
	GCA: axillary PET pos	GCA: axillary PET neg	Controls: axillary PET neg	Total		
Axillary US pos	53	5	0		Sensitivity	73% (61–82)
Axillary US neg	20	31	68		Specificity	100% (95–100)
Total	73	36	68	177[a]		
(B) Carotid artery						
	GCA: carotid PET pos	GCA: carotid PET neg	Controls: carotid PET neg	Total		
Carotid US pos	6	6	0		Sensitivity	14% (5–27)
Carotid US neg	38	62	68		Specificity	100% (95–100)
Total	44	68	68	180		
(C) Temporal artery						
	GCA: TA PET pos	GCA: TA PET neg	Controls: TA PET neg	Total		
TA US pos	25	35	1			
TA US neg	2	38	67			
Total	27	73	68	168[b]		
Patient level						
(D) GCA diagnosis (all assessed vessels)						
	GCA: LV or cranial PET pos	GCA: LV and cranial PET neg	Controls: LV and cranial PET neg	Total		
LV or TA US pos	49	2	1			
LV and TA US neg	4	1	33			
Total	53	3	34	90		
(E) c-GCA diagnosis (cranial vessels assessed)						
	GCA: cranial PET pos	GCA: cranial PET neg	Controls: cranial PET neg	Total		
TA US pos	31	9	1			
TA US neg	12	4	33			
Total	43	13	34	90		

US and PET of specific artery segment (A–C) and combinations of segments (D and E). Accuracy is only evaluated for US of LVs, since PET was not the predefined reference standard for c-GCA or overall GCA diagnosis. No control patients showed FDG uptake consistent with LV-GCA or c-GCA, and therefore these categories (PET pos controls) are not specified.

[a]Three missing values of axillary US in three different patients.

[b]In six patients, the PET/CT did not include temporal and maxillary artery. TA: temporal artery; LV: large vessel; pos: positive; neg: negative; FDG: ^{18}F-fluorodeoxyglucose.

the majority of patients had both a positive cranial PET and a positive temporal artery US, but the diagnosis was confirmed by a positive result in only one of the two imaging modalities in a significant fraction of patients. In four patients, the c-GCA diagnosis was not confirmed by either of the two modalities (Table 3E).

However, when all vessels of interest were assessed by both imaging modalities, in only one case the GCA diagnosis was not confirmed and in only six patients the diagnosis was based on only one of the two imaging tests (Table 3D). The one patient in whom a diagnosis was not confirmed by imaging had a positive TAB.

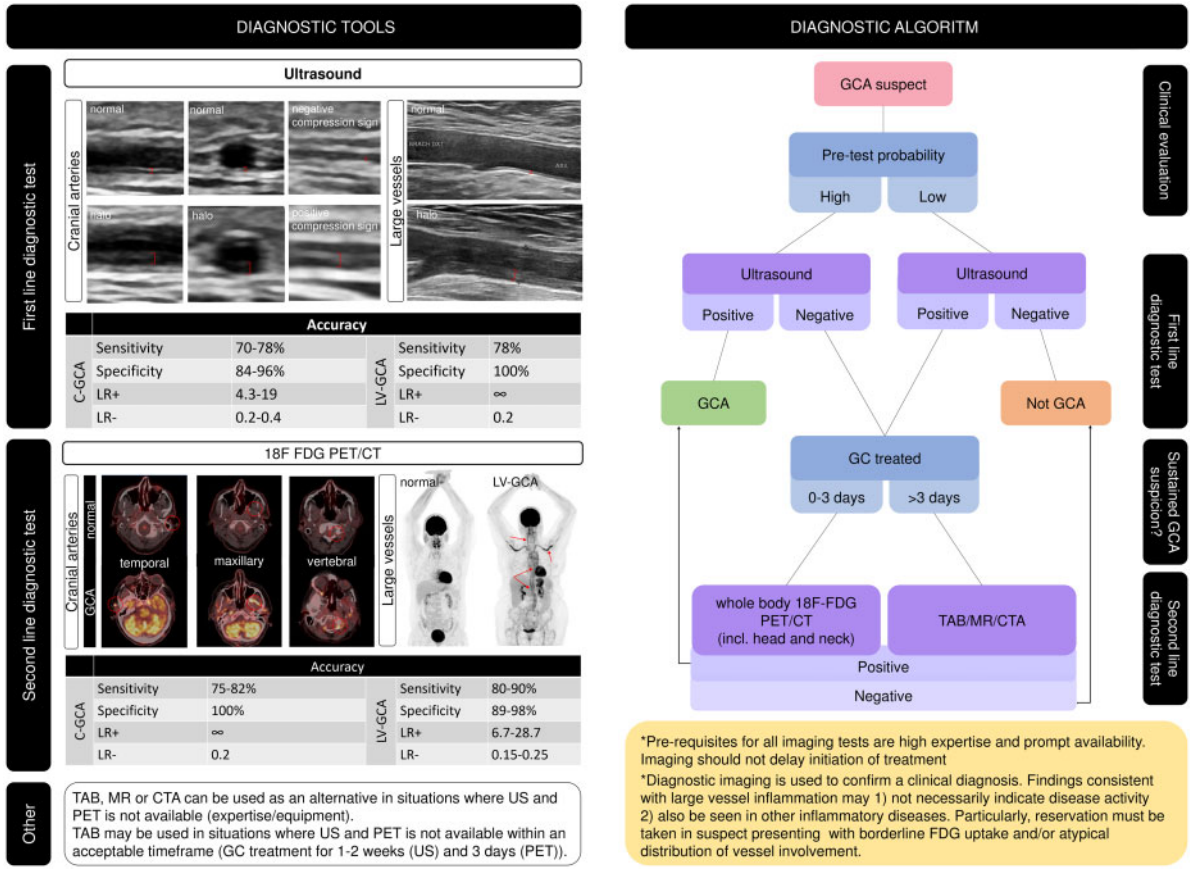
Discussion

In this prospective study of glucocorticoid-naïve new-onset GCA-suspected patients, we show that US examination of axillary arteries has an excellent diagnostic accuracy for PET-proven LV-GCA.

In line with our results, a recent retrospective study of 50 patients suspected of LV vasculitis of different aetiology found a sensitivity of 80% and specificity of 70% of LV US compared with PET, with the highest accuracy in axillary and subclavian arteries [33]. Considering LV inflammation in GCA patients, a good agreement between US and PET has also been reported in smaller studies of patients with US and/or clinically suspected LV involvement [14, 16].

An excellent diagnostic accuracy was found, despite the assessment of only a limited number of large vessels and although US visualizes morphologic changes, in contrast to PET, which is based on glucose metabolism assessment in the complete LV vascular tree. Moreover, the value of adding LV examination to temporal artery

Fig. 3 A novel diagnostic algorithm for the evaluation of patients suspected of GCA



Right: normal and vasculitic arteries by US and PET/CT. From meta-analysis of temporal artery US [38] and PET/CT [20] using ACR criteria, TAB or clinical diagnosis as reference, reports of the ability of PET to detect cranial GCA [21, 35] and the present study, estimates of diagnostic accuracy are provided. Left: EULAR recommendation states that concordant pre-test probability and US results confirm or dismiss GCA diagnosis. Contradictory results call for re-evaluation [11]. We suggest PET/CT as second-line test, preferably within 3 days of GC treatment [22]. c-GCA: cranial GCA; LV-GCA: large-vessel GCA; LR: likelihood ratio; GC: glucocorticoid; TAB: temporal artery biopsy.

US markedly increased sensitivity in our cohort, indicating that LV US should be part of routine examination.

An IMT cut-off differentiating normal from vasculitic segments may aid the interpretation of LVs. Axillary IMT cut-off 1.0–1.5 mm has been applied in previous studies [1, 14, 18]. An axillary IMT cut-off of 1.0 mm and 1.2 mm was established in two recent studies, using either the halo sign or the confirmation of LV involvement by cross-sectional imaging as reference [31, 34]. In agreement, we found that an axillary IMT cut-off of 1.0 mm correctly classified 83% of the axillary arteries using FDG PET/CT as reference.

The carotid artery is a predilection site of atherosclerosis. In the elderly patient, this could be another cause of both FDG uptake and increased IMT, explaining why IMT could not accurately differentiate PET-positive carotid segments from normal segments.

Recently, we reported high accuracy and interrater reliability of simple dichotomous assessment of cranial arteries on conventional FDG PET/CT in a case–control study [21]. The ability of PET/CT to detect cranial artery inflammation was subsequently reaffirmed in a cohort of GCA-suspected patients, reporting 9 of 12 TAB-positive patients showing cranial artery FDG uptake. The specificity of cranial artery assessment itself was not reported in that study [35]. In the present study, we confirm the high specificity of PET for the cranial arteries in GCA-suspected patients, thus further establishing a role of PET/CT in c-GCA diagnosis.

The availability and low cost of US makes it an appealing first-line imaging test not only in c-GCA, as recommended in the EULAR Recommendations for the Use of Imaging in the Diagnosis and Management of Large Vessel Vasculitis in Clinical Practice, but also in patients suspected of LV-GCA, and, hence, in GCA in general. EULAR recommendations inform that when the pre-test probability of GCA and the imaging result are concordant, other diagnostic tests are redundant. The pre-test probability, however, is yet to be specified. In case of discordancy, additional tests are required for diagnostic clarification [11]. Recently, the literature on FDG PET/CT diagnostic accuracy was extensively reviewed and procedural recommendations for FDG PET/CT patient preparation, image acquisition and interpretation for the diagnosis of LV-GCA were published [20]. Building on these reviews and recommendations [11, 20], our recent results on diagnostic accuracy of conventional PET in c-GCA [21], results of maintained diagnostic sensitivity of PET after short-term glucocorticoid treatment [22, 36, 37] and the results of the present study, we developed a novel algorithm for the evaluation of patients suspected of GCA. We suggest US as the first-line diagnostic test in all patients suspected of GCA. When a second-line diagnostic test is needed, we recommend FDG PET/CT including head and neck, provided glucocorticoid treatment has not been given for >3 days (Fig. 3). The benefits of PET/CT over other diagnostic tests are its high diagnostic accuracy in both GCA predilected vessel domains (cranial and supra-aortic LVs) [20, 21] and its ability to rule out alternative diagnoses such as cancer and infection [20, 21]. Prerequisites for both imaging tests are a high level of expertise and prompt availability. Based on availability, patients' clinical phenotype and/or the need for evaluation of structural lesions, TAB, MRI or CT angiography may be used as alternative diagnostic tests, as suggested by EULAR [11, 38].

To establish the until now most reliable estimates of the diagnostic accuracy of US for LV-GCA diagnosis, a large prospective cohort of patients suspected of GCA was evaluated, a highly accurate imaging test (PET/CT) was used as the reference for LV involvement and assessment of images was performed blinded to reference and index test, respectively. Moreover, only relatively easily accessible LVs were examined by US, making this evaluation feasible for clinical implementation.

Nevertheless, this study has some limitations. The eligibility criteria aimed to include patients presenting phenotypically as GCA and to reassure that potential arterial FDG uptake was attributed to GCA [39, 40] and indicative of ongoing inflammation [41–43]. Applying these criteria may have induced selection bias. However, US was performed for clinical indication in 11/12 of the excluded patients. Four excluded patients had a final diagnosis of GCA. On US examination, a large vessel halo was present in four and a temporal artery halo was present in three of these patients. In the remaining eight patients GCA was dismissed. US was performed in seven of eight non-GCA patients, revealing a positive temporal artery US in one patient (considered false positive) but a negative LV US in all patients. Selection bias therefore seems not to have had a major impact on our results.

Another potential limitation is that a reference standard for LV-GCA diagnosis does not exist. Nevertheless, it is well known that LV-GCA patients less often fulfil ACR criteria and often need imaging evaluation for diagnostic confirmation [8, 9, 12]. The applied cut-off for FDG intensity has shown high accuracy and interrater reliability [24, 25]. Although LV halos were not found in any control patients, they were found in a few GCA patients where the corresponding vessel was PET negative. A lower FDG intensity cut-off may have classified these segments correctly, but potentially at the expense of specificity. Also, infra-aortic LV FDG uptake, which was not alone considered as LV-GCA in this study, may indicate LV-GCA [10], but compromises specificity for LV-GCA diagnosis [16, 24, 44, 45]. None of our GCA patients presented isolated infra-aortic involvement and, in this regard, no patients were misclassified.

We evaluated PET of the cranial arteries for the diagnosis of c-GCA and compared the performance of PET and US in GCA diagnosis, as an exploratory analysis. However, the clinical diagnosis was established considering also the result of LV inflammation on PET, potentially favouring PET accuracy as compared with US.

In conclusion, our findings confirm the recommendation by EULAR to use US as the first-line diagnostic test

in patients suspected of c-GCA, but further suggest priority of US in LV-GCA-suspected patients. Based on EULAR recommendations and our present and recent findings, we propose a diagnostic algorithm for all patients suspected of GCA in which US of the temporal and axillary arteries is the first-line and whole-body FDG PET/CT is the second-line confirmatory test.

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Supplementary data

Supplementary data are available at *Rheumatology* online.

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