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Original article

Large-vessel giant cell arteritis: a cohort study

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Abstract

Objective. The aim of this study was to compare baseline variables, treatment and outcomes in patients with large-vessel GCA (LV-GCA), primarily of the upper extremities, with those with cranial disease (C-GCA).

Methods. All patients >50 years of age with radiographic evidence of subclavian LV-GCA diagnosed between 1 January 1999 and 31 December 2008 were identified and compared with those with biopsy-positive C-GCA diagnosed in the same period.

Results. The study included 120 LV-GCA patients and 212 C-GCA patients. Compared with C-GCA, patients with LV-GCA were younger [68.2 years (S.D. 7.5) *vs* 75.7 (7.4), $P < 0.001$] and had longer duration of symptoms at GCA diagnosis (median 3.5 *vs* 2.2 months, $P < 0.001$). A history of PMR was more common in LV-GCA patients (26% *vs* 15%, $P = 0.012$), but a smaller proportion had cranial symptoms (41% *vs* 83%, $P < 0.001$) and vision loss (4% *vs* 11%, $P = 0.035$). ACR classification criteria for GCA were satisfied in 39% of LV-GCA patients and 95% of C-GCA patients ($P < 0.001$). Compared with C-GCA, patients with LV-GCA had more relapses (4.9 *vs* 3.0/10 person-years, $P < 0.001$), higher cumulative corticosteroid (CS) doses at 1 year [11.4 g (S.D. 5.9) *vs* 9.1 (S.D. 3.7), $P < 0.001$] and required longer treatment (median 4.5 *vs* 2.2 years, $P < 0.001$).

Conclusion. Although patients with LV-GCA had a lower rate of vision loss, they had a higher relapse rate and greater CS requirements. The ACR criteria for GCA are inadequate for the classification of patients with LV-GCA.

Key words: giant cell arteritis, large-vessel vasculitis, imaging, treatment, prognosis.

Introduction

GCA is a systemic inflammatory vasculopathy that involves large and medium-sized arteries [1]. Involvement of the extracranial branches of the carotid artery gives rise to the classic cranial symptoms of GCA and sampling of the superficial temporal artery for histological evidence of vasculitis is considered the gold standard for diagnosis. However, GCA often also involves the aorta and its major branches and may lead to aortic aneurysm/dissection as well as large artery stenoses [2, 3]. A subset of patients with large-vessel GCA (LV-GCA), predominantly upper extremity arterial vasculitis, may have variable clinical presentations and diagnostic delay.

GCA appears to have a predilection for branches of the proximal aorta, in particular the subclavian, axillary and proximal brachial arteries [4, 5], while involvement of the branches of the abdominal aorta and lower extremity arteries is less common [5, 6]. The prevalence of extracranial GCA is not well defined. Aortic arch syndrome occurs in ~10–15% of patients [7]. Histological evidence of subclavian and axillary arterial involvement was reported in 26% of cases in one series [8]. Systematic screening of patients with radiographic imaging has yielded a variable prevalence of extracranial involvement, depending on the technique employed. In prospective studies of patients

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CLINICAL SCIENCE

with a new diagnosis of GCA, large-artery disease was seen in 29–83% [9–13].

To date, only one retrospective study has compared treatment, prognosis and long-term outcomes of GCA patients with upper extremity arterial involvement with those of patients with cranial GCA (C-GCA) and did not report any significant difference [14]. The survival of patients with GCA and large artery stenosis has been reported to be no different from that of patients with GCA without large artery stenosis [15, 16].

The aims of the present study were (i) to compare baseline variables that distinguish patients with LV-GCA from those with C-GCA and (ii) to compare the treatment, outcomes and prognosis of these two subtypes of GCA.

Methods

Study design

This is a retrospective study of patients with GCA diagnosed at the Mayo Clinic (Rochester, MN, USA) between 1 January 1999 and 31 December 2008. The study was approved by the Institutional Review Board at the Mayo Clinic.

Study definitions

For the purposes of the study we included and compared two cohorts of patients with GCA: the LV-GCA cohort and the C-GCA cohort. The LV-GCA cohort included patients with radiographic evidence of subclavian artery vasculitis attributed to GCA. Patients were identified using an electronic clinical notes search tool (Enterprise Data Trust portal). It was not required that the patients fulfil the 1990 ACR criteria for classification of GCA, with the exception that they were required to be >50 years of age [17].

According to imaging modality, subclavian involvement secondary to LV-GCA was defined as the presence of circumferential wall thickening and/or the presence of vascular stenosis/occlusion and/or vascular dilatation/aneurysm not attributed to atherosclerotic changes on CT angiography (CTA); the presence of circumferential wall thickening/wall oedema with or without contrast enhancement and/or the presence of vascular stenosis/occlusion and/or vascular dilatation/aneurysm not attributed to atherosclerosis on magnetic resonance angiography (MRA); subclavian arteries FDG uptake compatible with vasculitis [13] on 18F fluorodeoxyglucose-PET (FDG-PET); the presence of long segments of smooth arterial stenosis or smooth tapered occlusion and/or vascular dilatation/aneurysm without adjacent atherosclerotic plaques [18] on angiography; the presence of a dark, hypoechoic circumferential wall thickening (halo sign) not attributed to atherosclerotic changes on colour Doppler sonography (CDS) [9, 10].

The comparison cohort (C-GCA) included patients >50 years of age with a temporal artery biopsy (TAB) positive for GCA seen at the Mayo Clinic during the same period. A TAB showing vasculitis characterized by mononuclear cell infiltration or granulomatous inflammation, with or without multinucleated giant cells, was considered positive for GCA [17].

Exclusion

Patients with imaging studies of the subclavian arteries showing only changes of atherosclerosis (i.e. short, eccentric, focal stenosis, plaque, calcification) or fibromuscular dysplasia were excluded from the LV-GCA cohort, as well as patients with a diagnosis of Behcet's disease, Takayasu arteritis, sarcoidosis or other autoimmune CTD. Patients with radiographic evidence of vasculitis involving the primary branches of the aorta were excluded from the C-GCA cohort. Radiological evidence of aortitis and/or aortic dilatation without aortic branch involvement was not considered an exclusion criterion.

Data collection

We reviewed the available medical records of study participants from the date of GCA diagnosis to the end of the study follow-up (31 December 2010), the last visit at the Mayo Clinic or death. Only patients who were followed at the Mayo Clinic for at least 6 months after GCA diagnosis were considered for the outcomes analysis. Data abstracted included demographics, cardiovascular risk factors [hypertension, hyperlipidaemia, smoking (current/ever), diabetes mellitus, coronary artery disease], cardiovascular disease [angina or myocardial infarction, stroke or transient ischaemic attack (TIA), lower limb arterial disease] and previous diagnosis of PMR. Clinical features, laboratory and histology findings, medical treatment, vascular interventions and disease outcomes were also abstracted. Relapse was defined as the reappearance of symptoms of GCA and/or PMR associated with an increase in ESR and/or CRP. Isolated increase in inflammatory markers in the absence of other cause were considered relapses only if the treating rheumatologist increased the corticosteroid (CS)/immunosuppressive therapy with subsequent improvement.

Statistical analysis

Continuous data were presented as mean (S.D.) or median [interquartile range (IQR) (Q1, Q3)] and categorical variables as percentage. The Wilcoxon rank sum test was used to analyse continuous variables and chi-squared test was used for categorical variables. Kaplan–Meier methods and log-rank tests are used to estimate the rate of development of outcomes during follow-up, which is especially necessary because the length of follow-up differs between the two study cohorts. Relapse rate was calculated using person-year methods and differences in relapse rate between the groups were computed assuming the relapse rates followed a Poisson distribution.

Results

The cohorts

A total of 212 cases of biopsy-positive C-GCA and 120 cases of GCA with radiographically confirmed

TABLE 1 Baseline demographics of patients with cranial GCA and those with upper extremity arterial (large vessel) involvement

Variable	C-GCA ($n = 212$)	LV-GCA ($n = 120$)	P-value
Age at GCA diagnosis, mean (S.D.), years	75.7 (7.4)	68.2 (7.5)	<0.001
Female, *n* (%)	153 (72)	96 (80)	0.11
Time from symptom onset to diagnosis, median (Q1, Q3) months	2.2 (1.2, 3.7)	3.5 (2.0, 7.2)	<0.001
History of PMR prior to GCA diagnosis, *n* (%)	31 (15)	31 (26)	0.012
Prednisone use prior to GCA diagnosis, *n* (%)	23 (11)	20 (17)	0.13
Prednisone dose, mean (S.D.), mg	8.4 (6.0)	6.8 (3.9)	0.64
Duration of prior prednisone use, mean (S.D.), years	1.1 (1.3)	2.5 (2.6)	0.028
Hypertension, *n/N* (%)	105/212 (50)	56/116 (48)	0.83
Hyperlipidaemia, *n/N* (%)	86/212 (41)	47/119 (40)	0.85
Ever smoker, *n/N* (%)	75/206 (36)	53/119 (44)	0.15
Current smoker, *n/N* (%)	18/207 (9)	10/120 (8)	0.91
Diabetes mellitus, *n/N* (%)	14/200 (7)	4/120 (3)	0.21
CAD, *n/N* (%)	28/209 (13)	16/120 (13)	0.99

C-GCA: cranial GCA; LV-GCA: large-vessel GCA; CAD: coronary artery disease.

involvement of the subclavian arteries (LV-GCA) occurring during the study period were identified. Baseline demographic information for the two cohorts is presented in Table 1.

In 90 of 120 cases (75%) with LV-GCA, subclavian artery involvement was diagnosed at the same time as GCA. In 30 patients (25%), LV-GCA was diagnosed a mean of 2.6 years (S.D. 1.9) after the initial diagnosis of GCA. Twenty-one of the 30 patients were still on prednisone [mean daily dose 12.2 mg (S.D. 9.2)] when upper extremity arterial involvement was detected.

The majority of patients with LV-GCA [68/120 (57%)] had clinical symptoms and/or signs of upper extremity vascular insufficiency, while in 52 cases (43%) vasculitic involvement of the subclavian arteries was incidentally noted on imaging studies. Histological confirmation of GCA was available in 53 of 120 patients (44%) with LV-GCA. TAB was performed in 79 (66% of the LV-GCA cohort) patients and was positive for GCA in 41 (52%). In 19 patients (16% of the LV-GCA cohort), arterial tissue (other than TAB) was available for histopathological examination; in 14 (74%) findings were consistent with GCA.

Compared with patients with C-GCA, patients with LV-GCA were younger at diagnosis and had longer duration of symptoms prior to diagnosis. A greater proportion of patients with LV-GCA had a previous (>6 months prior) diagnosis of PMR compared with those with C-GCA (Table 2). Cranial symptoms and visual changes were less frequent in patients with LV-GCA compared with C-GCA, while findings of vascular insufficiency were more frequently observed (Table 2).

White blood cell count was significantly higher in patients with C-GCA compared with those with LV-GCA, while ESR, CRP, haemoglobin and platelet count did not differ between the two cohorts (Table 2). ACR classification criteria for GCA were satisfied in 39% of LV-GCA and 95% of C-GCA patients (Table 2).

Analysis restricted to the subset of C-GCA patients with negative large-vessel imaging

Imaging of the thoracic aorta and its branches was available in 70 of 212 patients (30%) with C-GCA. We performed subgroup analyses comparing these 70 patients (33%) with C-GCA and negative large-vessel imaging with the subset with LV-GCA. The results were unchanged with the exception of vision loss, which was noted in 9% with C-GCA who had imaging of the large vessels compared with 4% with LV-GCA ($P > 0.05$).

Imaging findings at LV-GCA diagnosis

LV-GCA was diagnosed by CTA in 59 patients (49%), MRA in 24 (20%), conventional angiography in 35 (29%), PET in 1 (1%) and CDS in 1 (1%). Table 3 shows the distribution of imaging findings at LV-GCA diagnosis. Thoracic aorta involvement was observed in 66 patients (56%), including aortic aneurysms in 14 patients. Of the 212 patients with C-GCA, 70 (33%) had imaging study of the thoracic aorta and its branches. None had vasculitic involvement of the aortic branches, but four had radiographic evidence of aortitis.

Treatment and outcomes

The mean daily dose of prednisone started at GCA diagnosis did not differ between patients in the two cohorts (Table 2). One hundred and three patients (86%) with LV-GCA and 167 patients (79%) with C-GCA had a follow-up period >6 months and were included in the outcomes analysis. Median duration of follow-up was 3.6 years for the LV-GCA group and 4.6 years for the C-GCA group ($P = 0.044$).

During the follow-up period, the relapse rate was higher in patients with LV-GCA compared with those with C-GCA (Table 4). Those with LV-GCA relapsed sooner than patients with C-GCA [time to first relapse, Kaplan–Meier method: median 0.8 (95% CI 0.6, 1.1) and 1.2 (1.0, 1.7) for LV-GCA and C-GCA, respectively, $P = 0.006$; Fig. 1].

Table 2 Comparison of clinical manifestations and laboratory findings in patients with cranial GCA and those with upper extremity arterial (large vessel) involvement

Variable	C-GCA ($n = 212$)	LV-GCA ($n = 120$)	*P*-value
Symptom, *n* (%)			
Any cranial symptoms	175 (83)	49 (41)	<0.001
Headache	137 (65)	39 (32)	<0.001
Jaw claudication	113 (53)	26 (22)	<0.001
Scalp tenderness	79 (37)	16 (13)	<0.001
Transient vision changes	37 (18)	12 (10)	0.07
Permanent vision changes	23 (11)	5 (4)	0.035
Diplopia	24 (11)	4 (3)	0.012
Constitutional symptoms	71 (33)	42 (35)	0.780
PMR symptoms	63 (30)	25 (21)	0.08
Upper extremity claudication	1 (0)	63 (52)	<0.001
Lower extremity claudication	7 (3)	11 (9)	0.023
RP	1 (0)	13 (11)	<0.001
Digital ulcerations secondary to ischaemia (upper extremity)	0 (0)	3 (2)	0.021
Physical examination findings, *n*/*N* (%)			
Temporal artery abnormalities	59/194 (30)	13/89 (15)	0.005
Vascular bruits	16/185 (9)	42/112 (38)	<0.001
Abnormal radial pulse	8/181 (4)	66/113 (58)	<0.001
Abnormal pedal pulse	25/156 (16)	14/111 (13)	0.44
Upper extremity blood pressure discrepancy	3/147 (2)	60/113 (53)	<0.001
Aortic regurgitation murmur	3/204 (1)	8/113 (7)	0.009
Laboratory			
ESR, mean (S.D.), mm/h	69.4 (32.6)	66.8 (37.0)	0.46
CRP, mean (S.D.), mg/l	63.9 (54.0)	64.3 (64.1)	0.66
Haemoglobin, mean (S.D.), g/dl	11.8 (1.6)	12.9 (11.2)	0.82
WBC count, mean (S.D.), $\times 10^3/\mu$l	9.5 (3.0)	8.4 (2.4)	0.002
Platelets, mean (S.D.), $\times 10^3/\mu$l	396.7 (131.9)	395.8 (138.7)	0.91
ACR criteria			
At least three ACR criteria, *n* (%)	202 (95)	47 (39)	<0.001
Number of ACR criteria met, median (IQR)	4.0 (3.0, 4.0)	2.0 (1.0, 3.0)	<0.001
Prednisone started at GCA diagnosis			
Prednisone dose, mean (s.d.), mg	52 (12)	54 (14)	0.054

C-GCA: cranial giant cell arteritis; LV-GCA: large-vessel giant cell arteritis; WBC: white blood cell; IQR: interquartile range (Q1, Q3).

Patients with LV-GCA also had a higher cumulative CS dose at 1 year than those with C-GCA and a greater proportion were treated with additional immunosuppressive therapy (Table 4). The median time to reach a daily dose of prednisone <10 mg (1.2 *vs* 0.9 years, log-rank $P < 0.001$) and to discontinue CS therapy (4.5 *vs* 2.2 years, log-rank $P < 0.001$) was significantly longer in LV-GCA compared with C-GCA. Similarly, the median time to reach a sustained discontinuation of CS therapy (for at least 6 months) was longer in patients with LV-GCA than in those with C-GCA (Fig. 2).

The prevalence of aortic aneurysm during follow-up was significantly higher in patients with LV-GCA compared with C-GCA (Table 4). There were no significant differences in the prevalence of the other outcomes evaluated during follow-up (angina or myocardial infarction, transient ischaemic attack or stroke and lower limb arterial disease; data not shown). The findings regarding relapses, cumulative CS doses and adjunctive immunosuppressive use were unchanged when restricting the analysis to the subset of 70 patients with C-GCA who had negative large-vessel imaging compared with those with LV-GCA.

Outcomes of patients with LV-GCA

Of the 68 patients with symptomatic upper extremity vascular insufficiency at LV-GCA diagnosis, 55 had a follow-up >6 months. At last clinical evaluation, the manifestations of upper extremity vascular insufficiency were improved in 30 patients (55%), resolved in 15 (27%), unchanged in 8 (15%) and worsened in none. Of the 52 patients without clinical signs of upper extremity vascular insufficiency at LV-GCA diagnosis, 47 had >6 months of follow-up. Forty-five patients (96%) did not develop signs of vascular insufficiency throughout the entire follow-up, while two patients (4%) developed upper extremity claudication with radial pulse abnormalities during follow-up.

Fifteen patients with LV-GCA underwent revascularization procedures; in eight, restenosis occurred in the

TABLE 3 Location and imaging findings at diagnosis of large-vessel involvement from GCA in 120 patients with large-vessel GCA

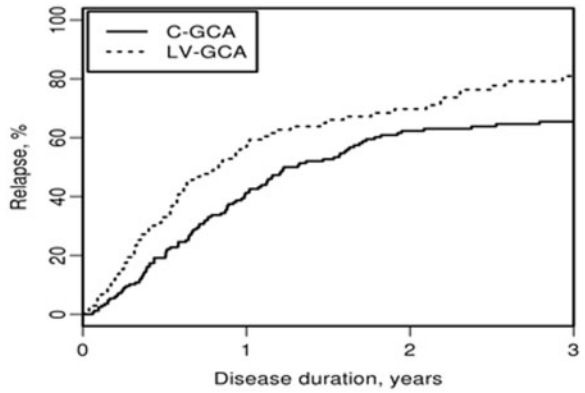
Vessel	Number visualized (*n*)	Wall thickening *n* (%)	Stenosis/ occlusion, *n* (%)	Aneurysm/ ectasia, *n* (%)	Any involvement, *n* (%)
Ascending aorta	119	23 (19)	0	23 (21)	41 (34)
Arch	119	39 (33)	0	12 (10)	49 (41)
Descending aorta	109	43 (39)	0	7 (6)	48 (44)
Abdominal aorta	64	28 (44)	1 (2)	3 (5)	31 (48)
Left carotid	118	40 (34)	11 (9)	0	49 (42)
Right carotid	118	10 (8)	10 (8)	0	19 (16)
Left vertebral	116	3 (3)	14 (12)	0	17 (15)
Right vertebral	114	0	16 (14)	0	16 (14)
Innominate	117	39 (33)	5 (4)	7 (6)	50 (43)
Left subclavian	117	65 (56)	65 (56)	11 (9)	109 (93)
Right subclavian	116	39 (34)	54 (47)	11 (9)	84 (72)
Left axillary	114	31 (27)	55 (48)	3 (3)	75 (66)
Right axillary	112	22 (20)	50 (45)	3 (3)	61 (54)
Left brachial	96	6 (6)	33 (34)	0	35 (36)
Right brachial	95	6 (6)	33 (35)	0	35 (37)
Celiac	109	7 (6)	5 (5)	2 (2)	13 (12)
Mesenteric (superior and inferior)	106	9 (8)	8 (8)	0	14 (13)
Left renal	108	4 (4)	2 (2)	1 (1)	6 (6)
Right renal	108	4 (4)	7 (6)	0	10 (9)
Left iliac	108	9 (8)	2 (2)	2 (2)	13 (12)
Right iliac	108	9 (8)	2 (2)	3 (3)	14 (13)
Left femoral	103	1 (1)	5 (5)	0	6 (6)
Right femoral	103	1 (1)	5 (5)	0	6 (6)

TABLE 4 Comparison of treatment and outcome variables in patients with cranial GCA and those with upper extremity arterial (large vessel) involvement

Outcome	C-GCA (*n* = 167)	LV-GCA (*n* = 103)	*P*-value[a]
Duration of follow-up, median (IQR), years	4.6 (2.5, 7.4)	3.6 (2.2, 6.4)	0.044
Relapses	252	215	
Relapse rate per 10 person-years, median (95% CI)	3.0 (2.6, 3.4)	4.9 (4.2, 5.6)	<0.001
Cumulative CS dose at 1 year, mean (S.D.), g	9.1 (3.7)	11.4 (5.9)	<0.001
Additional immunosuppressive therapy, *n* (%)	27 (16)	54 (52)	
Patients starting any immunosuppressive drug within 1 year of GCA diagnosis, KM method, median (95% CI), %	8 (4, 12)	32 (22, 42)	<0.001
Within 2 years	14 (8, 20)	46 (36, 56)	
Within 5 years	16 (10, 22)	57 (45, 69)	
MTX, *n*/*N* (%)	23/167 (14)	42/101 (42)	<0.001
AZA, *n*/*N* (%)	6/167 (4)	18/101 (18)	<0.001
Anti-TNF, *n*/*N* (%)	1/167 (1)	6/101 (6)	NA
MMF, *n*/*N* (%)	0/167 (0)	7/101 (7)	NA
CYC, *n*/*N* (%)	0/167 (0)	5/101 (5)	NA
Aortic aneurysm	9	14	
Rate of development of aortic aneurysm after GCA diagnosis, KM method, median (95% CI), %			0.005
1 year	2 (0, 4)	8 (2, 14)	
2 year	2 (0, 4)	9 (3, 15)	
5 year	3 (0,7)	15 (7, 23)	

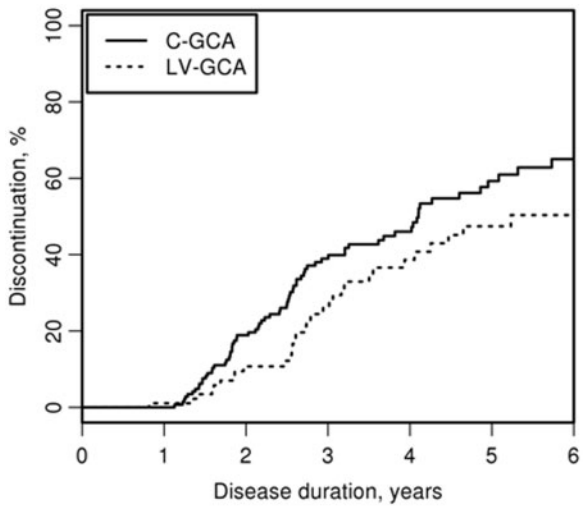
[a]Differences between groups were tested using rank sum tests for duration of follow-up and cumulative CS dose, Poisson methods for relapse rate and log-rank test for all others. For medications used by only one or no patients in a group, log-rank *P*-values were not available. C-GCA: cranial GCA; LV-GCA: large-vessel GCA; IQR: interquartile range (25th and 75th percentiles); KM: Kaplan–Meier estimate; NA: not available.

Fig. 1 Percentage of patients with at least one relapse by disease duration in patients with LV-GCA and C-GCA



Log-rank *P*-value = 0.006. C-GCA: cranial GCA; LV-GCA: large-vessel GCA.

Fig. 2 Percentage of patients who discontinued steroids for at least 6 months by disease duration in patients with LV-GCA and C-GCA



Log-rank *P*-value = 0.023. C-GCA: cranial GCA; LV-GCA: large-vessel GCA.

treated vessels during the follow-up period. Three of these eight patients required reintervention. Twelve patients with LV-GCA underwent surgical aortic aneurysm repair (10 ascending aorta, 1 ascending and arch, 1 thoracoabdominal).

Discussion

To our knowledge this is the largest study to compare patients with C-GCA with those with predominantly LV-GCA diagnosed at a single tertiary care centre. Rather than the classic GCA presentation with cranial symptoms, most patients with LV-GCA had symptoms of upper extremity vascular insufficiency. The diagnosis of vasculitis was delayed in patients with LV-GCA, likely due to the atypical clinical presentation. The treatment course and outcomes were strikingly dissimilar between the two cohorts, as patients with LV-GCA received higher doses of CSs, more immunosuppressive therapy and had more disease relapses.

Patients with LV-GCA were younger at diagnosis and had a longer duration of symptoms prior to diagnosis, a finding that has also been reported in previous studies [5, 9, 12]. Cranial and visual symptoms were less frequent in patients with LV-GCA, while findings of vascular insufficiency were more frequently observed, again in keeping with previous reports [5, 9, 10, 12, 19]. There was no difference in the frequency of constitutional symptoms or ESR values between the two study cohorts. In contrast, Brack *et al*. [5] reported less frequent constitutional symptoms and lower ESR values in patients with LV-GCA compared with those with C-GCA. White blood cell count was significantly higher in patients with C-GCA compared with those with LV-GCA. This is in contrast to a report by Both *et al*. [20], where high white blood cell count was associated with increased risk of upper extremity arterial stenosis.

In our study only 52% of patients with LV-GCA had a positive TAB, a frequency close to that found by Brack *et al.* (58%) [5] and Assie *et al*. (69.4%) [19]. In two other studies, Schmidt *et al*. [9] and Ghinoi *et al.* [10] did not report any difference in the frequency of positive TAB between LV-GCA and C-GCA patients, likely due to the different inclusion criteria used in the latter studies. Since only 79/120 (66%) of our LV-GCA patients underwent TAB (mainly those with cranial manifestations), we can assume that the frequency of positive TAB found in the present study [41/79 (52%)] was an overestimation of the real prevalence of positive TAB in LV-GCA.

The 1990 ACR criteria for GCA appear inadequate for classifying patients with LV-GCA. ACR classification criteria for GCA were satisfied in only 39% of LV-GCA patients, compared with 95% of C-GCA patients. Our data highlight that the current classification criteria [17] do not account for the clinical manifestations seen in patients with LV-GCA. Future efforts to develop classification criteria for GCA should consider that a subset of patients with GCA present with extremity claudication without cranial symptoms. Additionally, imaging findings that help diagnose such patients should be incorporated in future classification or diagnostic criteria. In this regard, FDG-PET is probably the most sensitive technique and has the advantage of visualizing all large vessels potentially involved in GCA (with the exception of the temporal and renal arteries) [21]. However, PET as a diagnostic modality in GCA has not been well studied. Furthermore, atherosclerosis can also lead to FDG uptake on PET scans [22] and PET is an expensive modality that is not uniformly available, which may limit its application as a diagnostic modality in GCA.

A greater proportion of patients with LV-GCA had a previous (>6 months prior) diagnosis of PMR compared with those with C-GCA. We hypothesize that in some patients PMR was not isolated, but was an expression of underlying LV-GCA. Recent studies reported a low frequency (1.3–9%) of positive TABs in patients with PMR without clinical manifestations of GCA [23, 24]. However, in 2003 Moosig *et al*. [25] reported increased FDG uptake of the aorta or its major branches in 12 of 13 patients with a new diagnosis of PMR (3 had a TAB positive for GCA) compared with 6 younger patients with highly inflammatory disease other than PMR. Subclavian and external carotid arteries were the best vascular areas in discriminating between active PMR and controls. In a more recent study, Blockmans *et al*. [26] showed vascular FDG uptake compatible with vasculitis on PET scans in 11 of 35 patients (31%) with a new diagnosis of PMR. In most patients, vascular uptake was seen in the subclavian arteries [26]. Cimmino *et al*. [27] also demonstrated FDG-PET evidence of vasculitis in ~37% of patients with CS-resistant PMR. These data are in keeping with our findings and suggest that ~25–30% of patients with PMR may have subclinical or clinically undetected LV-GCA.

LV involvement is generally an early manifestation of GCA [16]. In the present study LV involvement was present at GCA diagnosis in 75% of patients. Thoracic aorta involvement was observed in 66 patients (56%), including aortic aneurysms in 14 patients (12%).

Our study is the first to demonstrate that the prevalence of aortic aneurysm during follow-up was significantly higher in LV-GCA compared with C-GCA patients. This finding should be considered with caution, as patients with LV-GCA were followed more closely with imaging studies compared with C-GCA patients. However, if prospective studies confirm this findings, the systematic screening for LV involvement at GCA diagnosis will allow us to identify those patients at higher risk of aortic aneurysm.

Our study is one of the few to evaluate the treatment, outcomes and prognosis of patients with LV-GCA. In the study by Schmidt *et al*. [14], treatment factors, including mean duration of treatment and CS dose, were similar in 53 patients with LV-GCA and 53 patients with C-GCA. None of the patients required adjunctive immunosuppressive therapy [14]. In contrast, in the present study, while patients in both cohorts received similar prednisone dosages at diagnosis, patients with LV-GCA relapsed more frequently and earlier than those with C-GCA. Furthermore, patients with LV-GCA had a higher cumulative CS dose at 1 year and a greater proportion received additional immunosuppressive therapy compared with those with C-GCA.

While our findings need to be replicated, our study suggests that LV involvement in GCA is associated with more refractory clinical disease. Therefore systematic screening for LV involvement at GCA diagnosis could help identify patients who may be candidates for earlier introduction of additional immunosuppressive therapy. At present, the mainstay of GCA therapy is treatment with CSs, but adverse effects of CSs are observed in up to 86% of patients [28]. Therefore future clinical trials should specifically evaluate the role of novel immunosuppressive or biologic agents for the treatment of LV-GCA.

The prognosis was excellent in our cohort of patients with LV-GCA. No patients developed major ischaemic complications during the follow-up period. Of the patients with vascular insufficiency at diagnosis, the majority improved and none worsened. These results are in keeping with an earlier report by Schmidt *et al*. [14], in which all patients with symptoms at baseline improved after therapy. A more adverse prognosis was reported in the study by Assie *et al.* [19], in which signs and symptoms of upper/lower extremity vasculitis improved or resolved with medical therapy in 88.8% of patients with LV-GCA and worsened in 11.2%.

Our study has several limitations. First is the retrospective design, which relies on documentation in the medical records. Additionally, the treatment of patients and the addition of adjunctive immunosuppressive therapy was not standardized, but at the discretion of the treating physician. Because only 33% of patients with C-GCA underwent an imaging study of the large vessels during the course of the disease, we cannot exclude asymptomatic LV involvement in some patients with C-GCA, resulting in misclassification of the two study cohorts. In order to address this limitation, we performed additional analysis including only patients with C-GCA and negative LV imaging studies. Reassuringly, the findings remained unchanged with the exception of vision loss, which was not statistically different in the two groups. Our study also has a number of strengths, including the large size of the patient cohorts followed at a single tertiary care centre and the long duration of follow-up.

In conclusion, the spectrum of clinical manifestations in GCA is quite varied. On one end of the spectrum are patients with well-recognized cranial symptoms and a high frequency of positive TAB, who are recognized and diagnosed early. At the other end of the spectrum are patients with predominantly large-vessel involvement, who frequently lack cranial manifestations, and whose symptoms at disease onset are often subtle and non-specific, including symptoms of vascular insufficiency. These patients often require vascular imaging for confirmation of the diagnosis, which is often delayed. Many patients have overlapping features of cranial disease and large-vessel manifestations.

In general, patients with GCA are treated similarly, without consideration for whether they have C-GCA or LV-GCA. However, in this retrospective analysis, patients with LV-GCA had more features of refractory disease and might require more tailored therapy. Furthermore, patients with LV-GCA showed a higher prevalence of aortic aneurysm compared with C-GCA patients, indicating the need for more careful follow-up with more sensitive imaging studies for evaluation of the aorta. Finally, the 1990 ACR criteria for GCA do not perform well for the classification of LV-GCA.

Rheumatology key messages

- Clinical features at onset of large-vessel GCA differ from those of cranial disease GCA.
- Large-vessel GCA patients have higher relapse rate, greater corticosteroid requirements and increased prevalence of aortic aneurysm than cranial disease GCA patients.
- The ACR criteria for GCA are inadequate for the classification of patients with large-vessel GCA.

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