Different giant cell arteritis phenotypes may present distinct types of ischaemic complications

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Abstract

Objective

To determine if the subtype of vascular ultrasound (US) presentation is associated with different types of ischaemic complications (IC) in giant cell arteritis (GCA).

Methods

Retrospective observational analysis of GCA clinically confirmed patients referred to US fast-track clinics at two centres. All patients underwent baseline US of cranial and extracranial arteries (carotid, subclavian and axillary). Two patterns of IC were analysed: the occurrence of acute anterior ischaemic optic neuropathy (AION) or the presence of a non-AION pattern (including stroke, acute coronary syndrome, pulmonary embolism or peripheral artery disease) at diagnosis and in the following 3 months, excluding other potentially implicated causes.

Results

Of 188 clinically confirmed GCA patients, 43 (22.9%) had IC: 24 (12.8%) AION and 19 (10.1%) non-AION. Patients with AION more often exhibited US cranial involvement versus those with non-AION IC and without IC (100%, 63.2%, and 79.3%, respectively; p=0.009). Patients with AION less frequently presented signs of US large vessel (LV)-GCA than those with non-AION IC and without IC (25%, 63.2% and 55.2%, respectively; p=0.014). Patients with previous polymyalgia rheumatica (PMR) (p=0.049) or concomitant PMR symptoms at the time of diagnosis (p=0.014) showed less frequent AION. In contrast, patients with non-AION IC more frequently had positive LV-GCA US findings vs the other two groups (63.2%, 25% and 55.2%, respectively; p=0.014).

Conclusion

The subtype of vascular US presentation influences the IC in GCA. US cranial-GCA patients more frequently present AION, while predominantly US LV-GCA more frequently exhibit non-AION IC.

Key words

ultrasound, ischaemic complications, large-vessel vasculitis, giant cell arteritis, polymyalgia rheumatica

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Introduction

The most common vasculitis diagnosed in the elderly is giant cell arteritis (GCA), which predominantly affects the large arteries, particularly the branches of the carotid artery. Symptoms typically include diplopia or blurred vision, headache, scalp tenderness, jaw claudication/pain, polymyalgia rheumatica (PMR) symptoms, fever and/or constitutional symptoms. GCA can lead to serious complications if not treated promptly. Among the most concerning are ischaemic complications (IC), which are associated with significant morbidity and increased mortality (1-4). Identifying patients at risk of IC is crucial for improving long-term outcomes. Over the last decade, several studies have assessed risk factors for IC, such as visual complications or stroke, in patients with GCA, yielding varying conclusions (4-17). Some studies have reported an association with less pronounced clinical or laboratory systemic inflammation (6, 7, 9, 13-16). Others have also described a positive association between traditional atherosclerosis risk factors or established vascular disease and IC-related GCA (5, 6, 8, 9, 11, 12, 14-17). The value of ultrasound (US) in the diagnosis of GCA and, as a consequence, the risk of IC has been studied over the last decades. However, individualisation of the risk based on the subtype of vascular involvement as a predictor of different types of IC has not yet been established.

The recently updated 2023 EULAR recommendations on the use of imaging in large-vessel vasculitis prioritise US of the temporal and axillary arteries as first-line imaging test for evaluating patients with suspected GCA (18). Indeed, its implementation in clinical practice could improve the diagnosis of GCA (19, 20). However, these recommendations do not endorse routine imaging for follow-up and to date there remain very few studies that examine the prognostic value of US in predicting ischaemic complications in patients with GCA (21).

Our main objective was to determine if the subtype of vascular US presentation is associated with different types of IC in GCA patients.

Methods

Patients

This was a retrospective observational study that included patients referred to US fast-track clinics at two academic centres for the screening of possible GCA over a 4-year period. Per protocol, patients with suspected GCA were referred to this US clinic for examination within 72 hours. For the purposes of this study, only consecutive patients with clinically confirmed GCA at 6 months of follow-up were included for analysis. This study was performed under routine clinical practice conditions.

Data collection

The following variables were collected from the electronic health records: demographics (*e.g.* age and sex), presenting symptoms (headache, scalp tenderness, jaw claudication, visual symptoms and ocular ischaemia diagnosis by an ophthalmologist, fever, previous PMR diagnosis, PMR symptoms at GCA onset, and constitutional symptoms, previous use of glucocorticoids, and laboratory variables (*e.g.* C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), haemoglobin, and platelets). The gold standard for GCA diagnosis was clinical confirmation by the treating clinician after at least 6 months of follow-up. IC was categorised as either the occurrence of acute anterior ischaemic optic neuropathy (AION) (diagnosed by an ophthalmologist or neurologist) or non-AION (including stroke, acute coronary syndrome, pulmonary embolism or peripheral artery disease) at diagnosis and in the following 3 months, and after excluding other potentially implicated causes. Other complementary tests, such as temporal artery biopsy or other imaging tests (PET/CT), were requested at the clinician's discretion if necessary for the diagnosis and they were not performed systematically.

Ultrasound assessment

The three temporal arteries (TA) segments (common superficial trunk and its parietal and frontal branches) and extracranial (carotid, subclavian and distal and proximal axillary) arteries were bilaterally evaluated by US in all patients within 24 hours per protocol (excluding

Table I. Baseline characteristics, clinical and laboratory variables according to the presence and type of ischaemic complications.

	All patients n=188	No ischaemic complication n=145 (77.1%)	AION n=24 (12.8%)	Non-AION IC n=19 (10.1%)	*p*
Demographics					
Age, mean (SD)	78.2 (8.5)	77.7 (8.9)	81.1 (5.8)	78.6 (8.5)	0.183
Female, n (%)	88 (46.8%)	69 (47.6%)	10 (41.7%)	9 (47.4%)	0.864
Clinical variables					
Headache, n (%)	147 (78.2%)	115 (79.3%)	18 (75%)	14 (73.7%)	0.788
Scalp tenderness, n (%)	46 (24.5%)	38 (26.2%)	3 (12.5%)	5 (26.3%)	0.344
Jaw claudication, n (%)	47 (25%)	37 (25.5%)	6 (25%)	4 (21.1%)	0.915
Constitutional symptoms, n (%)	100 (53.2%)	81 (55.9%)	10 (41.7%)	9 (47.4%)	0.376
Fever, n (%)	29 (15.4%)	25 (17.2%)	0 (0%)	4 (21.1%)	0.074
Concomitant PMR symptoms, n (%)	91 (48.4%)	77 (53.1%)	5 (20.8%)	9 (47.4%)	**0.014**
Previous PMR diagnosis, n (%)	53 (28.2%)	45 (31%)	2 (8.3%)	6 (31.6%)	**0.049**
Abnormal TA clinical examination, n (%)	42 (22.3%)	31 (21.4%)	5 (20.8%)	6 (31.6%)	0.594
SCORE CVR score, mean (SD)	21.8 (14.7)	20.9 (14.8)	25.5 (13)	24 (15.4)	0.275
Laboratory findings					
CRP (mg/L), mean (SD)	36.4 (54.3)	40.3 (57.6)	26.3 (48.8)	20.1 (24.6)	0.194
ESR (mm/h), mean (SD)	58.1 (34.2)	56.1 (35.1)	73.7 (25.8)	54.4 (32.5)	0.072
Haemoglobin (g/dL), mean (SD)	13.4 (11)	13.8 (12.5)	12 (1.8)	12 (2)	0.658
Platelets 10^9/L, mean (SD)	326.5 (128.1)	334.7 (126)	297.1 (151.4)	302.6 (108.1)	0.288
Histology					
Temporal artery biopsy positive, n/total number of biopsies performed (%)	21/50 (42%)	15/38 (39.5%)	6/8 (75%)	0/4 (0%)	**0.037**
Outcomes					
Relapse at 6 months follow-up, n (%)	24 (12.8%)	16 (11%)	5 (20.8%)	3 (15.8%)	0.377

AION: acute anterior ischaemic optic neuropathy; PMR: polymyalgia rheumatica; CRP: C-reactive protein; ESR: erythrocyte sedimentation rate; US: ultrasound; LV: large-vessel; SD: standard deviation; CVR: cardiovascular risk.

weekends with delays up to 72 h). The patient, in a supine position, was examined by three experienced ultrasonographers (EdM, IM-H and JM-C) using an EsaoteMyLab8 (Esaote, Genoa) with a 12–18 MHz (for TA) and 6–15 MHz transducer (for extracranial arteries) and an Esaote Mylab X8 system (Esaote, Genoa) with a 12–25 MHz (for TA) and 4–15 MHz transducers (for extracranial arteries). The distal axillary arteries were scanned from the axillary fossa. The focus was positioned 5 mm below the skin for the TA and 2–3 cm for the axillary arteries. The pulse repetition frequency was 2–3 kHz. The colour box was set at an angle between sound waves and the artery at <60°. The presence of a halo and/or compression sign in TA or the presence of a halo in extracranial arteries in the absence of atherosclerosis was considered sufficient for a positive US examination (22). The ultrasonographer was not blinded to the clinical information of the patients.

Statistical analysis

Quantitative data were described as the mean (standard deviation, SD) and qualitative variables as the absolute frequency (percentages). A Chi-square test or Fisher's exact test was used to analyse the differences between proportions; a Student's t test was used for comparisons between the means. All tests were two-sided; *p*-values <0.05 were considered statistically significant. SPSS software (v. 23.0; IBM, USA) was used for statistical analysis.

Ethical approval

This study was performed in accordance with the ethical standards of the responsible committee on human experimentation and the Helsinki Declaration of 1975, as revised in 1983. The research protocol was approved by the Research Ethics Committee of the Hospital General Universitario Gregorio Marañón (JMC08-RHEUM0722) and the Research Ethics Committee of the Hospital Universitario La Paz (PI3040). Informed written consent was not mandatory for patient participation in this study.

Results

Patient characteristics

A total of 188 patients with GCA clinical confirmation referred to fast-track clinics were included for analysis; 88 (46.8%) were female, with a mean age of 78.2 years. A total of 172 (91.5%) patients fulfilled the ACR/EULAR 2022 GCA classification criteria (23). Table I summarises the baseline characteristic, as well as the clinical and laboratory variables of the patients included. A TA biopsy was performed per clinician criteria in 50 patients, with positive results in 21 (42%) of the GCA patients. Regarding the most notable clinical variables, 147 patients (78.2%) presented headache, 100 (53.2%) constitutional symptoms, 88 (46.8%) morning stiffness in proximal girdles suggestive of PMR, 53 (28.2%) had a previous diagnosis of PMR, 47 (25%) jaw claudication and 29 (15.4%) fever.

GCA vascular subtypes

A total of 183 (97.3%) patients presented positive US findings. Of these, 151 (80.3%) patients had cranial involvement, 85 (45.2%) had isolated cranial involvement, 98 (52.12%) had positive large-vessel (LV)-CGA, and 32 (17%) had isolated positive LV-GCA. Among the 5 (2.7%) patients with GCA diagnosis and negative US, one had positive FDG-PET/CT findings and the

Table II. Ultrasound findings of GCA patients according to the presence and type of ischaemic complications.

	All patients n=188	No ischaemic complication n=145 (77.1%)	AION n=24 (12.8%)	Non-AION IC n=19 (10.1%)	*p*
US findings					
Positive US, n (%)	183 (97.3%)	140 (96.6%)	24 (100%)	19 (100%)	0.467
Positive cranial GCA US, n (%)	151 (80.3%)	115 (79.3%)	24 (100%)	12 (63.2%)	**0.009**
Positive isolated cranial GCA US, n (%)	85 (45.2%)	60 (41.4%)	18 (75%)	7 (36.8%)	**0.007**
Positive large-vessel-GCA US, n (%)	98 (52.1%)	80 (55.2%)	6 (25%)	12 (63.2%)	**0.014**
Isolated positive large-vessel-GCA US, n (%)	32 (17%)	25 (17.2%)	0 (0%)	7 (36.8%)	**0.006**
Mixed cranial + large-vessel GCA US, n (%)	66 (35.1%)	55 (37.9%)	6 (25%)	5 (26.3%)	0.328

others, despite negative imaging, were presumed to have GCA based on the evaluation of the attending physician.

Ischaemic complications

Patient characteristics according to IC type are shown in Table I. A total of 43 (22.9%) patients had an IC at diagnosis or in the following 3 months of follow-up, 24 (12.8%) an AION and 19 (10.1%) a non-AION IC (9 had experienced a stroke, 4 acute coronary syndrome, 3 peripheral artery disease, 2 pulmonary embolism and 1 ischaemic colitis). Patients with AION more frequently showed evidence of US cranial involvement (100%) *versus* those with non-AION IC (63.2%) and without IC (79.3%); p=0.009. All patients with AION presented positive cranial US findings (18 with isolated cranial involvement and 6 with mixed involvement), whereas none presented isolated LV US. In contrast, patients with non-AION IC more frequently presented signs of US LV-GCA (63.2%) *versus* those with AION (25%) or without IC (55.2%), p=0.014. Regarding a previous diagnosis of PMR, 2 (8.3%) patients with AION had a previous diagnosis of PMR *versus* 6 (31.6%) with non-AION and 6 (31%) without IC; p=0.049. Patients with morning stiffness in proximal girdles suggestive of PMR at GCA diagnosis less frequently presented AION (20.8%) *versus* the other groups (p=0.014). No significant differences were observed in the frequency of PMR diagnosis (30.6% *vs*. 25.6%; p=0.695) or PMR symptoms at the time of diagnosis (51% *vs*. 45.6%; p=0.454) between patients with and without LV-GCA US, respectively.

Discussion

We have demonstrated a potential association between different patterns of vascular US involvement and distinct types of IC in patients with GCA. Our findings suggest that a vascular US pattern may serve as a valuable indicator for identifying specific subgroups of GCA patients at higher risk for specific types of IC. Understanding these associations could aid in developing more targeted and personalised approaches for the management and prevention of IC in individuals diagnosed with GCA. Traditionally, GCA and PMR have been considered distinct inflammatory conditions, albeit closely related, with similar epidemiological distributions (24, 25). The relationship between GCA and PMR is complex, with a significant percentage of patients having both conditions (26). Both conditions are thought to be part of the same spectrum of disease (GCA-PMR spectrum disease) with different risks and potential treatments (27). Approximately half of GCA patients experience PMR either at the time of diagnosis or during relapse, while about a fifth may have a history of PMR (27). A recent study has demonstrated that the risk of relapse in patients with PMR varies depending on the presence or absence of subclinical vasculitis (28). Therefore, knowledge gaps in the relationship between PMR and GCA persist (26), and the prognostic role, including the frequency of ischaemic complications, remains unknown when PMR precedes or coexists at the onset of GCA.

We can differentiate three patterns of US vascular involvement in GCA patients: the classic cranial pattern (cranial GCA), the extracranial large-vessel pattern (LV-GCA) and a combination of these two patterns (mixed-GCA) (29, 30). While studies of GCA have traditionally focused on temporal arteries, there is growing evidence that LV involvement is more frequent than previously thought. In this context, we have determined that patients with AION more frequently exhibited US cranial involvement compared to those with non-AION IC or without IC. Moreover, all patients with AION presented cranial involvement (isolated or mixed), whereas none presented isolated LV-GCA. Our results are in line with previous studies that have identified cranial symptoms as predictors of visual involvement in GCA (4, 31, 32). In contrast, patients with non-AION IC more frequently presented signs of US LV-GCA *versus* those with AION or without IC. These data are novel and demonstrate that in LV-GCA, there is also an associated risk of IC, including severe forms such as cerebrovascular accidents. Strokes and non-AION IC are more frequent when LV involvement is also present. However, a lack of cranial involvement in mixed forms can increase the risk of non-AION IC. While encouraging, these new findings should be further tested in larger cohorts. After AION, stroke is the second most frequent ischaemic complication in GCA, followed by acute coronary syndrome and peripheral artery disease. Previously identified predictors of stroke include male gender (5, 16), presence of visual symptoms (5 ,9, 16), hypertension (5, 16), smoking (16), and absence of anaemia (5, 9, 16).

On the other hand, the presence of PMR in patients with GCA has traditionally been associated with a reduced risk of IC, although such patients tend to relapse more frequently during follow-up (24). According to our results, patients with previous or concomitant PMR symptoms may be at less risk of developing AION. It is important to note

that while PMR symptoms are usually associated with LV-GCA, in our cohort no differences were observed in the frequency of a previous PMR diagnosis or PMR symptoms at the time of GCA diagnosis between patients with and without US LV-GCA, respectively. Some limitations affecting our study should be noted.

First, it was retrospective in nature and there may be some recorded inaccuracies or incomplete data. Second, the small sample size of each group may limit the study's statistical power. Third, the ultrasonographer was not blinded to the clinical data.

Another potential limitation is that intra- and inter-observer reliability was not specifically investigated for this study, although previous reliability studies have been performed within the same research group (33). Finally, the arteries of the lower limbs were not included in the US examination, which could limit the detection of LV-GCA.

In summary, different patterns of vascular involvement based on US are associated with varying ischaemic complications in patients with GCA. Predominantly cranial-GCA patients more frequently experience AION, whereas predominantly LV-GCA patients have a higher incidence of non-AION ischaemic complications. This underscores the importance of additional validation and replication studies across different settings in order to strengthen the robustness of these findings in various contexts and patient groups.

Take home messages

- The different vascular subtypes of GCA are associated with distinct types of IC.
- US cranial-GCA patients more frequently present AION IC.
- US LV-GCA patients more frequently present non-AION IC.

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