Diagnostic Assessment Strategies and Disease Subsets in Giant Cell Arteritis: An International Observational Cohort

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ABSTRACT

Objective:

To determine if giant cell arteritis (GCA) subsets based on temporal artery and extracranial involvement are associated with distinct clinical profiles or reflect differential diagnostic assessment.

Methods:

Patients with GCA, recruited from an international cohort, were divided into four subsets based on a temporal artery (TA) abnormality [positive temporal-artery biopsy or halo-sign on temporal-artery ultrasound] and/or imaging evidence of large-vessel involvement, as follows: 1) *both* large-vessel involvement and TA abnormality [TA(+)/LV(+) GCA]; 2) TA abnormality without large-vessel involvement [TA(+)/LV(-) GCA]; 3) large-vessel involvement without TA abnormality [TA(-)/LV(+) GCA]; and 4) clinically diagnosed GCA without large-vessel involvement or TA abnormality [TA(-)/LV(-) GCA].

Results:

Out of 941 patients, 75% had a TAB, 57% had LV imaging, and 35% had TA-US. GCA subsets had distinct clinical profiles independent of diagnostic assessment strategies. TA(+)/LV(-) GCA was the most common subset (51%) and had the highest burden of visual changes and other cranial ischemic symptoms. TA(-)/LV(-) GCA (26%) was most like TA(+)/LV(-) GCA with a high prevalence of visual changes and other cranial ischemic symptoms but with a higher burden of musculoskeletal symptoms. TA(-)/LV(+) GCA (12%) was younger, with a high burden of vascular, constitutional, and pulmonary symptoms. TA(+)/LV(+) GCA (11%) was older with a high prevalence of cranial ischemic symptoms like TA(+)/LV(-) GCA and had a high prevalence of lower-limb vascular abnormalities and constitutional symptoms like TA(-)/LV(+) GCA.

Conclusion:

Despite variability in diagnostic assessment strategies for GCA, patients can be divided into unique, clinical subsets based on temporal and extracranial artery involvement.

Introduction

Giant cell arteritis (GCA) is a rare form of vasculitis that causes inflammation within the medium and large arteries. GCA is a heterogeneous disease (1). Clinical symptoms and the extent of arterial involvement often vary between patients. GCA was traditionally thought to be confined to the cranial arteries; however, many patients with GCA also have evidence of large-vessel involvement by angiography (2-5). Patients with large-vessel involvement often present with different clinical features than patients with cranial GCA, but the extent to which patients have overlapping versus distinct cranial and extra-cranial disease is not well characterized (5-8).

A temporal artery biopsy (TAB) with mononuclear cell infiltrate or granulomatous inflammation remains the gold standard of diagnosis in GCA. Although highly specific by definition, the sensitivity of TABs has decreased over time highlighting that many patients with GCA are diagnosed without histological evidence of arteritis (9-12). Patients suspected of having GCA are increasingly diagnosed using temporal artery ultrasound (TA-US) (13). A peri-luminal hypo-echoic halo in the temporal artery has been proposed as a diagnostic equivalent of a positive TAB (14). Additionally, large-vessel imaging has become an increasingly common form of diagnostic assessment in GCA. A substantial percentage of patients with GCA, with and without a positive TAB, have large-vessel involvement with estimates ranging from 20-67% by angiography, 83% by 18F-fluorodeoxyglucose positron emission tomography (FDG-PET) imaging, and 100% by autopsy (2-5, 15-17).

Patients can receive a diagnosis of GCA based on a combination of cranial and large-vessel assessment. With the expansion of diagnostic modalities in GCA, it remains poorly understood the extent to which cranial and large-vessel GCA are distinct entities or if co-occurrence is under detected. The objectives of this study were to detail the assessment strategies currently employed to diagnose GCA using data collected within a large international, observational cohort and to determine if GCA subsets, defined by

temporal artery biopsy (TAB) and vascular imaging, are associated with distinct clinical profiles or merely reflect differential diagnostic testing.

METHODS

Patient selection

The Diagnostic and Classification Criteria in Vasculitis (DCVAS) is an international, observational cohort of patients with vasculitis (18, 19). Patients were enrolled less than five years since time of diagnosis. Only physician-submitted cases with a diagnosis of GCA confirmed by expert panel review were included in this study.

Clinical variables

Comprehensive demographic, clinical, and vascular-imaging data were collected using standardized forms. Data was available in the following domains: visual changes and other ischemic cranial symptoms, pulmonary, musculoskeletal, and constitutional symptoms, vascular abnormalities, and laboratory findings. Clinical variables were recorded if present by time of diagnosis.

Vascular abnormalities

Temporal artery physical examination abnormalities were defined as tenderness, diminished or absent pulse, and/or a nodular, cord-like temporal artery. Blood pressure was recorded in both arms and blood pressure differences between the arms were categorized as less than or greater than 10 mmHg. Pulse abnormality was defined as diminished or absent pulse in either the upper limbs (subclavian, axillary, brachial, or radial arteries) or lower limbs (femoral, popliteal, posterior tibial, or dorsalis pedis arteries). A bruit in the abdominal aorta, carotid, subclavian, axillary, or renal arteries was recorded.

Laboratory findings

The maximum values of the erythrocyte sedimentary rate (ESR) and c-reactive protein (CRP) since disease onset were recorded. Anemia was defined as hemoglobin <10g/dL, hypoalbuminemia as albumin <30g/L, and thrombocytopenia as platelets $<100 \times 10^9$ per liter.

Temporal artery biopsies

Temporal artery biopsies were performed at the discretion of the physician. A biopsy was defined as active vasculitis per local review and recorded by the submitting physician

Large-vessel and temporal artery imaging

Ultrasonography of the temporal arteries was performed in a subset of patients. Halo sign was defined as a peri-luminal hypo-echoic halo in the temporal artery. Halo sign was assessed per local review and recorded by the submitting physician.

Large-vessel involvement was assessed in a subset of patients by a combination of angiography, ultrasonography, or 18F-fluorodeoxyglucose positron emission tomography (FDG-PET) imaging. Clinical radiologists or nuclear medicine physicians at each participating institution assessed vascular imaging data. Angiographic and ultrasound damage was defined as stenosis, occlusion, or aneurysm. FDG-PET scans were assessed according to local practices (20). Large-vessel involvement was defined as having arterial damage or abnormal FDG-uptake within 13 arterial territories of interest: right and left carotid, subclavian, axillary, iliofemoral, and renal arteries; mesenteric arteries; and ascending, descending, and abdominal aorta.

Subset definitions

Patients were divided into four subsets based on temporal artery biopsy, temporal-artery ultrasound, and/or large-vessel imaging findings. Patients with evidence of *both* large-vessel involvement on imaging and either a positive TAB or halo-sign on TA-US were classified as **TA(+)/LV(+) GCA**. Patients with a TAB with definite vasculitis or halo-sign on TA-US without evidence of large-vessel involvement on imaging were classified as **TA(+)/LV(-) GCA**. Patients with evidence of large-vessel involvement on imaging without a positive TAB or halo sign on TA-US were classified as **TA(-)/LV(+) GCA**. Patients with a clinical diagnosis of GCA without evidence of large-vessel involvement on imaging, positive

TAB, or halo sign on TA-US were classified as **TA(-)/LV(-) GCA**. Clinical differences were studied between the four subsets.

Since TAB, TA-US, and large-vessel imaging assessment was performed at the discretion of the treating physician, patients could have received different diagnostic assessment. To determine the extent that differences between the subsets were related to clinical differences versus diagnostic bias from differential assessments, analyses were repeated in a restricted cohort of patients that received both temporal-artery assessment (TAB or TA-US) and large-vessel imaging.

Statistical methods

Chi-square, Mann-Whitney, and Kruskal-Wallis tests were used as appropriate. A p value <0.05 defined statistical significance. Nominal logistic regression was used to study the associations between the clinical decision to undergo a specific diagnostic test and clinical features of disease. All analyses were performed using Graphpad Prism V.7.0a (GraphPad, La Jolla, California, USA).

RESULTS

Subject characteristics

A total of 941 patients with GCA were included. Demographic information is listed in **Table 1**.

Diagnostic assessment strategies in the DCVAS cohort

Patients received vascular assessment at the discretion of the submitting physician. Overall, 328 (35%) patients had TA-US, 705 (75%) had a TAB, 534 (57%) had large-vessel imaging, and 431 (45.8%) had both large-vessel and temporal-artery assessment (**Table 1**). Only 33 patients (3.5%) did not have any diagnostic testing performed beyond clinical assessment (**Supplementary Table 1**).

Diagnostic assessment strategies by demographics

Diagnostic assessment differed between patients based on demographic information, including age and gender. Male patients were more likely to receive a TAB compared to female patients (Male: 81.4% vs Female: 71.6%; p=0.001) (**Supplementary Table 2**). In logistic regression models, male patients were more likely to have a TAB compared to female patients independent of cranial ischemic symptoms, age at diagnosis, and temporal-artery abnormality on physician exam (**Supplementary Table 3**). There was no gender preference in the rate of TA-US (Male: 36.8% vs Female: 33.9%, p=0.38) or large-vessel imaging (Male: 57.7% vs Female: 56.3%, p=0.70) (**Supplementary Table 2**). Male and female patients were equally likely to have a positive TAB (Male: 61.6% vs Female: 64.3%, p=0.51) and evidence of large-vessel involvement on imaging (Male: 36.2% vs Female: 42.6%, p=0.16). Male patients were more likely to have a halo-sign on TA-US than female patients (Male: 85.0% vs 75.4%, p=0.05).

Patients who received a TAB were older (73.4 years vs 70.5 years, p<0.0001) and patients who received large-vessel imaging were younger (71.9 years vs 73.8 years, p=0.0009). There was no difference in age between patients that did and did not receive a TA-US (72.8 years vs 72.6 years, p=0.71).

Diagnostic assessment by continent

Diagnostic assessment differed between patients based on the continent they were seen. The rate of TAB did not differ between continents (North America: 82.8%, Europe: 73.1%, Asia: 82.8%, Oceania: 88.9%) (**Figure 1**). The majority of TA-US were performed at European centers (North America: 2.7%, Europe: 41.0%, Asia: 13.8%, Oceania: 0.0%). Large-vessel imaging was performed in about half of patients from North American, European, and Asian centers, but less commonly done in Oceanian centers (North America: 58.6%, Europe: 57.7%, Asia: 51.7%, Oceania: 11.1%).

Patients with multiple forms of diagnostic assessment

The majority of patients had multiple forms of diagnostic assessment. Regardless of TAB results, approximately 60% of patients had vascular imaging studies performed in addition to the biopsy (**Supplementary Table 1**). Vascular imaging was performed in 86.1% of patients who did not have a TAB and confirmed disease in 70.0% of these patients (**Supplementary Table 1, Figure 2**). TA-US was rarely used alone as a form of vascular assessment. Only 1.1% of patients had TA-US without another form of vascular assessment compared to the 10.9% of patients that had only LV-imaging and 32.3% of patients that had only TAB.

The results of TAB were not strongly associated with large-vessel imaging or TA-US results (**Figure 2**). Patients with a negative or positive TAB were equally likely to have evidence of large-vessel involvement on imaging (Positive TAB: 31% vs Negative TAB: 27%, p=0.54). Similarly, patients with a negative or positive TAB were equally likely to have a halo sign on TA-US (Positive TAB: 82% vs Negative TAB: 76%, p=0.38).

Subsets of patients with giant cell arteritis

Subsets of patients were defined by cranial and large-vessel involvement. Patients were characterized into one of four subsets as follows: 480 (51.0%) patients as TA(+)/LV(-) GCA; 245 (26.0%) as TA(-

)/LV(-) GCA; 116 (12.3%) as TA(-)/LV(+) GCA; and 100 (10.6%) as TA(+)/LV(+) GCA. Demographics and assessment strategies within each group are provided in **Table 1**.

Subset diagnosed by temporal artery biopsy

In the GCA-TA subset, 430 (89.6%) patients had a TAB, 225 (46.9%) had a TA-US, 228 (47.4%) had large-vessel imaging, and 227 (47.3%) had both large-vessel and temporal-artery assessment. By definition, all patients in this subset had evidence of temporal artery involvement, 379 (79.0%) had a positive TAB and 203 (42.3%) had a halo sign on TA-US (**Supplementary Table 4**). Compared to other subsets, patients with TA(+)/LV(-) GCA had the highest prevalence of temporal-artery abnormalities on physical examination (TA(-)/LV(-) GCA: 38.9% vs TA(+)/LV(-) GCA: 57.0% vs TA(+)/LV(+) GCA: 51.0% vs TA(-)/LV(+) GCA: 10.3%; $p<0.0001$). Patients in the TA(+)/LV(-) GCA subset had a high prevalence of vision changes (TA(-)/LV(-) GCA: 41% vs TA(+)/LV(-) GCA: 42% vs TA(+)/LV(+) GCA: 25% vs TA(-)/LV(+) GCA: 19%; $p<0.0001$) and other ischemic cranial symptoms (TA(-)/LV(-) GCA: 91% vs TA(+)/LV(-) GCA: 92% vs TA(+)/LV(+) GCA: 78% vs TA(-)/LV(+) GCA: 44%; $p<0.0001$) including amaurosis fugax, sudden ongoing visual loss, jaw claudication, scalp tenderness, and new onset headache.

Patients with TA(+)/LV(-) GCA were older (TA(-)/LV(-) GCA: 71.0 vs TA(+)/LV(-) GCA: 74.1 vs TA(+)/LV(+) GCA: 74.2 vs TA(-)/LV(+) GCA: 68.6 years; $p<0.0001$), less likely to be female (TA(-)/LV(-) GCA: 70.9% vs TA(+)/LV(-) GCA: 64.2% vs TA(+)/LV(+) GCA: 64.0% vs TA(-)/LV(+) GCA: 75.9%; $p=0.049$), and had a low prevalence of vascular abnormalities, laboratory abnormalities, and constitutional and musculoskeletal symptoms compared to other subsets (**Table 1**).

Subset diagnosed by clinical symptoms without confirmatory histology or imaging findings

In the TA(-)/LV(-) GCA subset, most patients had a TAB (n=174, 71.0%), few patients had a TA-US (n=22, 9.0%), 90 (36.7%) patients had large-vessel imaging, and 59 (24.1%) patients had both large-vessel and temporal-artery assessment (**Table 1**). Patients with TA(-)/LV(-) GCA were most similar to patients with TA(+)/LV(-) GCA (**Supplementary Table 4, Figure 3)**. These patients had a similarly high prevalence of vision changes (TA(-)/LV(-) GCA: 41% vs TA(+)/LV(-) GCA: 42%; p=0.81) and other ischemic cranial symptoms (TA(-)/LV(-) GCA: 91% vs TA(+)/LV(-) GCA: 92%; p=0.57) compared to TA(+)/LV(-) GCA, including sudden ongoing visual loss, jaw claudication, scalp tenderness, and headache. Patients with TA(-)/LV(-) GCA, however, were younger (TA(-)/LV(-) GCA: 71.0 vs TA(+)/LV(-) GCA: 74.1; p<0.0001) and more likely to be female (TA(-)/LV(-) GCA: 70.9% vs TA(+)/LV(-) GCA: 64.2%; p=0.08) than patients with TA(+)/LV(-) GCA (**Table 1**). Patients with TA(-)/LV(-) GCA had a high prevalence of musculoskeletal symptoms including morning stiffness greater than one-hour (TA(-)/LV(-) GCA: 22.1% vs TA(+)/LV(-) GCA: 14.1% vs TA(+)/LV(+) GCA: 14.0% vs TA(-)/LV(+) GCA: 16.4%; p=0.05), morning stiffness in the hips and thighs (TA(-)/LV(-) GCA: 21.3% vs TA(+)/LV(-) GCA: 15.6% vs TA(+)/LV(+) GCA: 15.0% vs TA(-)/LV(+) GCA: 12.1%; p<0.0001), and muscle tenderness (TA(-)/LV(-) GCA: 12.7% vs TA(+)/LV(-) GCA: 6.0% vs TA(+)/LV(+) GCA: 13.0% vs TA(-)/LV(+) GCA: 6.0%; p<0.0001).

Subset diagnosed by large-vessel imaging

In the TA(-)/LV(+) GCA subset, 27 (23.3%) patients had a TAB, 20 (17.2%) patients had a TA-US, and 45 (38.8%) patients had both large-vessel and temporal-artery assessment (**Table 1)**. By definition, all patients in this group had large-vessel imaging. Patients with TA(-)/LV(+) GCA had significantly fewer ischemic cranial symptoms and temporal artery abnormalities compared to the other subsets (**Supplementary Table 4, Figure 3)**. These patients were younger (p<0.0001) and more likely to be female (p=0.049) than the other subsets. Patients with TA(-)/LV(+) GCA had a high prevalence of vascular symptoms and examination findings (TA(-)/LV(-) GCA: 25% vs TA(+)/LV(-) GCA: 20% vs TA(+)/LV(+) GCA: 37% vs TA(-)/LV(+) GCA: 49%; p<0.0001) including arm claudication, leg

claudication, vascular bruit, upper limb pulse abnormality, lower limb pulse abnormality, absent blood pressure in one or more arms, and a blood pressure difference between arms greater than 10mmHg. Patients with TA(-)/LV(+) GCA had the highest prevalence of pulmonary symptoms (TA(-)/LV(-) GCA: 10% vs TA(+)/LV(-) GCA: 12% vs TA(+)/LV(+) GCA: 16% vs TA(-)/LV(+) GCA: 23%; p=0.003) including dyspnea and non-productive cough. Patients with TA(-)/LV(+) GCA had a high prevalence of constitutional symptoms (TA(-)/LV(-) GCA: 46% vs TA(+)/LV(-) GCA: 48% vs TA(+)/LV(+) GCA: 68% vs TA(-)/LV(+) GCA: 65%; p<0.0001) including night sweats, fever, and weight loss.

Subset diagnosed by positive temporal-artery and large-vessel imaging abnormalities

In the TA(+)/LV(+) GCA subset, 74 (74%) patients had a TAB and 61 (61%) patients had a TA-US (**Table 1**). By definition, all patients had large-vessel imaging and temporal-artery assessment. All patients had evidence of temporal artery involvement, 68 (68%) had a positive TAB and 55 (55%) had a halo sign on TA-US (**Supplementary Table 4**). The clinical profile of TA(+)/LV(+) GCA had features similar to TA(+)/LV(-) GCA and TA(-)/LV(+) GCA, as well as features that were not seen in either subset (**Figure 3, Supplementary Table 4**). Patients with TA(+)/LV(+) GCA were older (TA(+)/LV(-) GCA: 74 vs TA(+)/LV(+) GCA: 74, p=0.91), less likely to be female (TA(+)/LV(-) GCA: 64% vs TA(+)/LV(+) GCA: 64%, p=0.96), and had a high prevalence of temporal artery abnormalities (TA(+)/LV(-) GCA: 57% vs TA(+)/LV(+) GCA: 51%, p=0.32) similar to TA(+)/LV(-) GCA. Patients with TA(+)/LV(+) GCA had a high prevalence of ischemic cranial symptoms (TA(+)/LV(-) GCA: 92% vs TA(+)/LV(+) GCA: 78% vs TA(-)/LV(+) GCA: 44%; p<0.0001), significantly higher than TA(-)/LV(+) GCA but lower than TA(+)/LV(-) GCA, including jaw claudication, scalp tenderness, and new onset headache. Although the overall prevalence of ischemic cranial symptoms was similar between TA(+)/LV(+) GCA and TA(+)/LV(-) GCA, patients with TA(+)/LV(+) GCA were less likely to have visual changes (TA(+)/LV(-) GCA: 42% vs TA(+)/LV(+) GCA: 25%; p=0.002) including amaurosis fugax and sudden ongoing visual loss compared to patients with TA(+)/LV(-) GCA.

Patients with TA(+)/LV(+) GCA and TA(-)/LV(+) GCA had a similarly high prevalence of vascular abnormalities (TA(+)/LV(+) GCA: 37% vs TA(-)/LV(+) GCA: 49%; p=0.08) particularly vascular bruit, blood pressure differences between arms, and lower-limb abnormalities, including lower limb claudication and lower limb pulse abnormality (**Figure 3, Supplementary Table 4**). However, TA(+)/LV(+) GCA had a significantly lower prevalence of upper limb vascular symptoms and examination abnormalities compared to TA(-)/LV(+) GCA, including arm claudication (TA(+)/LV(+) GCA: 1% vs TA(-)/LV(+) GCA: 20%, p<0.0001) and upper limb pulse abnormality (TA(+)/LV(+) GCA: 4% vs TA(-)/LV(+) GCA: 23%, p<0.0001). Patients with TA(+)/LV(+) GCA had a high prevalence of constitutional symptoms (TA(+)/LV(+) GCA: 68% vs TA(-)/LV(+) GCA: 65%; p=0.66) similar to TA(-)/LV(+) GCA, including night sweats, fever, and weight loss.

Patients with TA(+)/LV(+) GCA had the highest prevalence of laboratory abnormalities and the highest frequency of elevated acute-phase reactants when compared to other subsets (TA(-)/LV(-) GCA: 34% vs TA(+)/LV(-) GCA: 29% vs TA(+)/LV(+) GCA: 38% vs TA(-)/LV(+) GCA: 28%; p=0.2), including anemia, hypoalbuminemia, thrombocytopenia, ESR, and CRP (**Supplementary Table 4**).

Patients with diagnostic assessment of both the cranial and large arteries

Analyses were repeated in the 431 (46%) patients that had both large-vessel and temporal-artery assessment. Among this restricted cohort, 340 (79%) patients had TAB and 258 (60%) patients had TA-US. 64% of patients were female with an average age at disease onset of 72.8 years. All four clinical subgroups were again observed: 59 (14%) patients with TA(-)/LV(-) GCA, 227 (53%) patients with TA(+)/LV(-) GCA, 100 (23%) patients with TA(+)/LV(+) GCA, and 45 (10%) patients with TA(-)/LV(+) GCA (**Supplementary Table 5**). There was no difference in prevalence of the TA(+)/LV(-) GCA (51% vs 53%, p=0.57) and TA(-)/LV(+) GCA (12% vs 10%, p=0.31) subgroups in the whole cohort compared to the restricted cohort. Patients in the restricted cohort were less likely to have TA(-)/LV(-) GCA (14% vs 26%, p<0.0001) and more likely to have TA(+)/LV(+) GCA (23% vs 11%, p<0.0001).

In the total cohort of patients, TA(-)/LV(-) GCA was defined by a high prevalence of temporal artery abnormalities, ischemic cranial symptoms, visual changes, and morning stiffness, with a low prevalence of vascular abnormalities (**Figure 4**). These differences, except for the low prevalence of vascular abnormalities, were again observed in the restricted cohort. Patients with TA(-)/LV(-) GCA in the restricted cohort had a high prevalence of leg claudication (13.6% vs 4.9%; $p<0.0001$) and arterial bruit (15.3% vs 7.0%; $p=0.04$) compared to TA(-)/LV(-) GCA patients in the total cohort (**Supplementary Table 5)**. In the total cohort of patients, TA(+)/LV(-) GCA were older, more likely to be male, with a high prevalence of temporal artery abnormalities, ischemic cranial symptoms, and visual changes, and a low prevalence of vascular abnormalities and constitutional symptoms (**Figure 4**). These differences, except for the higher male prevalence, remained consistent in the restricted cohort. In the total cohort of patients, TA(-)/LV(+) GCA were younger and more likely to be female, with a high prevalence of upper and lower limb vascular abnormalities, and pulmonary and constitutional symptoms. These differences, except for the female prevalence, remained in the restricted cohort (**Supplementary Table 5**). In the total cohort of patients, TA(+)/LV(+) GCA were older and more likely to be male with a high prevalence of temporal artery abnormalities, ischemic cranial symptoms, lower limb vascular abnormalities, and constitutional symptoms (**Figure 4**). These differences, except for higher male prevalence, remained in the restricted cohort (**Supplementary Table 5**).

Discussion

Diagnostic assessment in GCA is rapidly changing as non-invasive vascular imaging techniques become increasingly available to categorize the extent of arterial involvement. Data from this study demonstrate how clinicians across the world use different diagnostic assessment strategies to assess arterial involvement in GCA. Although TAB is still the most common form of diagnostic assessment, non-invasive techniques such as ultrasonography, angiography, and PET imaging are increasingly used to assess disease in GCA. Patients are now more frequently recognized who have isolated or overlap cranial and large-vessel involvement. This study also details the characteristics of clinical subsets based on documented involvement of the cranial or large arteries. Besides differences in the extent of vascular involvement, patients in these subsets have different clinical profiles that likely reflect underlying biological differences. These findings should inform clinicians on the clinical variability among patients with GCA and aid in researching more homogenous patient populations.

Temporal artery biopsy remains the diagnostic gold standard for GCA; however, the sensitivity of TAB has declined in recent years (21). Decreasing sensitivity is due in part to the use of vascular imaging as a diagnostic surrogate to biopsy to detect arterial involvement in and beyond the temporal arteries. Three quarters of patients with a diagnosis of GCA in the DCVAS cohort underwent a TAB to diagnose GCA, but a third of these biopsies were not diagnostic. Of those with a non-diagnostic TAB, 32.6% had evidence of vascular involvement by vascular imaging and 67.4% were diagnosed based on clinical symptoms alone. Vascular imaging was used as an alternative method to diagnose GCA in a quarter of patients who did not have a TAB.

Vascular imaging techniques are being used to complement TAB and to capture the full extent of arterial disease. Over half of the patients who had a TAB had additional vascular imaging, independent of TAB results. Approximately 50% of patients with a TAB had large-vessel imaging and about 30% had a TA-US. Regional practices strongly influenced diagnostic assessment strategies, as TA-US was performed

mostly at European centers. Patients who had a TA-US also typically had a concomitant TAB. Patients with a negative or positive TAB were equally likely to have a halo-sign on TA-US, suggesting that TA-US and TAB may identify different aspects of disease.

Clinical subsets in GCA have been proposed to account for the significant clinical heterogeneity seen amongst patients with GCA. Patients with large-vessel involvement often present with different clinical features than patients with cranial GCA, but the extent to which patients have overlapping versus distinct cranial and extra-cranial disease is not well characterized. In this study, clinical subsets were created *a priori* based on documented cranial and large-vessel involvement. Different clinical profiles were observed in patients with GCA based on whether or not disease was observed in the cranial or large arteries. Restriction of analyses to a subset of patients who had comprehensive temporal artery and large-vessel assessment confirmed that these clinical differences were not simply the product of differential diagnostic testing. However, some bias in diagnostic assessment was also observed. Women were less likely than men to undergo a biopsy of the temporal artery to confirm a diagnosis of GCA independent of differences in the presenting features of disease.

TA(+)/LV(-) GCA represents patients with a traditional GCA clinical profile. These patients had a high burden of cranial ischemic symptoms and visual changes, and had limited evidence of large-vessel involvement. Patients with isolated large-vessel involvement differed substantially from patients with isolated temporal-artery involvement in their demographics and presenting clinical features. As previous studies have suggested, patients with isolated large-vessel involvement more closely resembled patients with Takayasu's arteritis, the other major form of large-vessel vasculitis which predominately affects young women. Patients with TA(-)/LV(+) GCA were younger, more likely to be female, and had a high burden of vascular abnormalities, constitutional, and pulmonary symptoms.

A subset of patients with GCA have overlap cranial and large-vessel disease leading to speculation that the extent arterial involvement may be under detected in patients with isolated cranial or large-vessel involvement. However, in the DCVAS cohort, patients with overlap cranial and large-vessel involvement had unique clinical associations, confirming that patients with overlap disease represent an independent subgroup that is not merely due to under detection of arterial involvement in the other subgroups. Patients with overlap disease were older with a high prevalence of cranial ischemic symptoms, similar to patients with isolated cranial disease, and had a high prevalence of lower-limb vascular abnormalities, bruits, and constitutional symptoms, similar to patients with isolated large-vessel disease. Unlike the other subgroups, patients with overlap disease had the highest prevalence of laboratory abnormalities and constitutional symptoms. Similar to prior studies, patients with large-vessel involvement, including those with overlap disease, were less likely to have visual changes, (6).

In the DCVAS cohort, almost all patients had some form of arterial assessment, but a quarter of patients did not have diagnostic confirmation of involvement of either the cranial or extra-cranial arteries. The clinical profile of these patients was nearly indistinguishable from patients with TA(+)/LV(-) GCA. These patients also had an increased burden of polymyalgia rheumatica (PMR)-like symptoms. Even in the face of negative diagnostic assessment, these patients were diagnosed with GCA, most likely due to the suggestive pattern of cranial ischemic symptoms and PMR-like symptoms.

This study has potential limitations to consider. Diagnostic and imaging assessment was not standardized across the cohort. Temporal artery or large-vessel involvement may have been under detected. However, when analyses were repeated in the restricted cohort, the same pattern of clinical symptoms was observed in the four subsets. Additionally, standardized definitions for a diagnostic TAB or halo sign on TA-US were not used and were defined at the discretion of the submitting physician. Large-vessel imaging was not standardized in the DCVAS cohort. Different rates of large-artery involvement in GCA have been described based on modality, and there is no gold standard for assessing large-vessel involvement in

GCA. There is circularity in subgrouping based on documented arterial involvement since vascular assessment may be driven by the presenting clinical symptoms. However, in the restricted cohort, where patients had cranial and large-vessel assessment, all four subgroups were observed with a similar pattern of clinical symptoms. The majority of participating centers in the DCVAS cohort are tertiary, research hospitals; therefore, diagnostic assessment may not be representative of general practice. Long-term outcome data was not available in the DCVAS cohort, but prior studies have suggested that patients with TA(-)/LV(+) GCA are more treatment refractory (7).

With the widespread adoption of vascular imaging into clinical practice, clinical variability is increasingly appreciated amongst patients with GCA. Previous studies have shown that patients with GCA can differ in their systemic inflammatory response, extent of arterial involvement, and treatment response (6) and suggest that there are distinct subgroups of GCA with potentially divergent disease etiology. Identifying subgroups may lead to stratified clinical decision making and enable research into differences in disease pathology. In this study, subsets of patients with GCA have distinct clinical profiles based on involvement of the cranial or large arteries. The extent to which differences in biologic mechanisms of disease underlie these subsets is unknown. Prospective studies to assess potential differences in disease risk factors, response to treatment, and long-term outcomes amongst subsets of patients with GCA are warranted.

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