CLINICS

CLINICAL SCIENCE

Giant cell arteritis: a multicenter observational study in Brazil

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OBJECTIVE: To describe demographic features, disease manifestations and therapy in patients with giant cell arteritis from referral centers in Brazil.

METHODS: A retrospective cohort study was performed on 45 giant cell arteritis patients from three university hospitals in Brazil. Diagnoses were based on the American College of Rheumatology classification criteria for giant cell arteritis or temporal artery biopsy findings.

RESULTS: Most patients were Caucasian, and females were slightly more predominant. The frequencies of disease manifestations were as follows: temporal headache in 82.2%, neuro-ophthalmologic manifestations in 68.9%, jaw claudication in 48.9%, systemic symptoms in 44.4%, polymyalgia rheumatica in 35.6% and extra-cranial vessel involvement in 17.8% of cases. Aortic aneurysms were observed in 6.6% of patients. A comparison between patients with biopsy-proven giant cell arteritis and those without temporal artery biopsies did not yield significant differences in disease manifestations. All patients were treated with oral prednisone, and intravenous methylprednisolone was administered to nearly half of the patients. Methotrexate was the most commonly used immunosuppressive agent, and low-dose aspirin was prescribed to the majority of patients. Relapses occurred in 28.9% of patients, and aspirin had a protective effect against relapses. Females had higher prevalences of polymyalgia rheumatica, systemic manifestations and jaw claudication, while permanent visual loss was more prevalent in men.

CONCLUSIONS: Most of the clinical features of Brazilian giant cell arteritis patients were similar to those found in other studies, except for the high prevalence of neuro-ophthalmic manifestations and permanent blindness in the Brazilian patients. Aspirin had a protective effect on relapses.

KEYWORDS: Giant Cell Arteritis; Glucocorticoids; Methotrexate; Multicenter Study; Vasculitis.

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INTRODUCTION

Giant cell arteritis (GCA) is a systemic chronic vasculitis of large- and medium-sized vessels that mainly affects the cranial branches of arteries originating from the aortic arch in individuals who are more than 50 years of age (1,2). The highest annual incidence rates of GCA are found in Scandinavian countries and the northern United States, where there are many people of Scandinavian descent; the GCA incidence rates are lower in southern European countries, such as in Italy and Spain. The lowest incidence rates have been reported in Japan, Turkey and Israel and among native Alaskans (2-5). GCA case series have been published from different countries (e.g., Saudi Arabia, Mexico, Tunisia and India) and population groups (e.g., African American, Asian and Hispanic patients from the United States) (3-6).

To our knowledge, the only data on the epidemiology of GCA in the Brazilian population are two case reports and a small study evaluating anterior ischemic optic neuropathy (AION) in GCA patients (7-9). Therefore, this study aimed to describe the demographic features, disease manifestations, therapy and outcomes of Brazilian patients with GCA.

No potential conflict of interest was reported.

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MATERIALS AND METHODS

Study design and protocol

We performed a retrospective cohort study to evaluate Brazilian patients who fulfilled the American College of

Rheumatology (ACR) Criteria for GCA (10) and who were under regular follow-up in three tertiary university hospitals (Universidade Federal de São Paulo, Universidade de São Paulo and Universidade do Estado do Rio de Janeiro). The study was approved by the institutional ethics committees, and data were collected between 2009 and 2010.

Patients' medical records were reviewed to collect data according to a standardized protocol. Demographic features included age at diagnosis and at study date, gender, ethnicity and information on ancestry. We recorded information about systemic symptoms, temporal and occipital headache, jaw claudication, neuro-ophthalmic manifestations of GCA, partial or complete vision loss secondary to GCA neuro-ophthalmic manifestations, neurological manifestations, such as transient ischemic attacks, ischemic stroke and peripheral neuropathy, symptoms of polymyalgia rheumatica (PMR), involvement of large- and/or middle-sized vessels and erythrocyte sedimentation rate (ESR) at disease onset. Neuro-ophthalmic manifestations of GCA were defined as amaurosis fugax, diplopia, AION or posterior ischemic optic neuritis (PION) and central retinal artery occlusion.

A positive temporal artery biopsy was considered when vasculitic findings, such as inflammatory infiltrate on an arterial wall with or without granuloma and multinucleated giant cells, were described upon pathological examination of temporal artery specimens. The investigation of extra-cranial artery involvement was performed by computed tomography angiography or magnetic resonance angiography when patients presented vascular signs and symptoms, such as limb claudication, vascular bruits or a decrease in arterial pulses, or when imaging studies performed for other purposes displayed arterial abnormalities. When the aorta and/or its main branches were affected by aneurysms, stenosis or arterial occlusions, this was regarded as extra-cranial artery involvement. Comorbidities and/or complications of secondary glucocorticoid therapy presented by GCA patients were recorded. Disease relapse was considered when the patient presented typical manifestations of GCA associated with an increased ESR (> 50 mm/1st hour) after excluding secondary causes, such as infections. Deaths that occurred during the follow-up period were recorded. The GCA disease course was classified (according to the presence or absence of relapses) as monophasic or relapse-remitting.

We evaluated medical therapies, including prednisone use, pulse therapy with methylprednisolone, methotrexate or another immunosuppressive agent, antiplatelet therapy and statins. Patients with active GCA and visual symptoms were initially treated with high-dose prednisone (1 mg/kg/day) with intravenous pulse methylprednisolone (1 g/day for three days), while patients presenting uncomplicated forms of GCA were initially treated with prednisone (40 mg/day). Prednisone tapering began after the resolution of active GCA symptoms and was performed at the physician's discretion. Methotrexate was added after the first relapse as a steroid-sparing agent and to prevent more disease relapses. If patients could not tolerate methotrexate, it was replaced by another immunosuppressive agent, such as azathioprine or oral cyclophosphamide.

Statistical analysis

SPSS software (version 15.0) was used to carry out the statistical analyses. Categorical data are presented as total numbers and percentages, and numerical data are presented as the means, medians, standard deviations, ranges or as 95% confidence intervals (CIs). Comparisons between groups were performed using a chi-square test or Fisher's exact test for categorical data and Student's t-test or Mann-Whitney U-test for continuous variables. Univariate and multivariate logistic regression models analyzed associations with relapses, and results are expressed as odds ratios (ORs) and 95% CIs.

RESULTS

Demographic features and GCA manifestations

The median ages of the 45 GCA patients at the time of study and at disease onset were 78.0 (95% CI: 73.2–78.4) and 73.0 (95% CI: 68.7–73.7) years, respectively. In 23 (51.1%) patients, diagnoses of GCA were made between 70 and 79 years of age, and no patients had onset of disease manifestations before age 50 or after age 90. The mean follow-up period was 54.9 ± 41.9 months. The female-to-male ratio was 1.8:1.0, and most GCA patients were Caucasians (86.7%), while 13.3% were mestizos. Among Caucasian GCA patients, 69.2% were of Portuguese, 25.6% of Italian and 5.2% of Spanish descent.

Table 1 describes the prevalence of GCA manifestations in this sample of Brazilian patients. Although all patients fulfilled the ACR criteria for GCA, a temporal artery biopsy was performed on only 18 (40.0%) patients, and it displayed features of vasculitis in 16 of those (88.8%) cases. No significant differences in demographic features, disease manifestations or ESR were found between patients with biopsy-proven GCA and those classified as GCA according to the ACR criteria (Table 2). All patients with neuro-ophthalmic manifestations developed AION, and it was preceded by amaurosis fugax in 11 cases. No patients developed diplopia, PION or central retinal artery occlusions. In all but one patient with permanent visual loss, amaurosis developed at disease onset in patients presenting neuro-ophthalmic manifestations who did not show improvement in visual acuity after commencing glucocorticoids. Only one patient developed permanent visual loss (unilateral amaurosis) during a relapse. Among patients with extra-cranial artery involvement, aortic aneurysms were found in three patients (6.6%), the thoracic aorta was involved in two patients (4.4%), and the abdominal aorta

Table 1 - Manifestations of giant cell arteritis among Brazilian patients.

Manifestation	Frequency
Systemic manifestations, n (%)	20 (44.4)
Fever, n (%)	14 (31.1)
Anorexia, n (%)	13 (28.9)
Weight loss, n (%)	17 (37.8)
Temporal headache, n (%)	37 (82.2)
Occipital headache, n (%)	6 (13.3)
Jaw claudication, n (%)	22 (48.9)
Anterior ischemic optic neuritis, n (%)	31 (68.9)
Amaurosis fugax, n (%)	11 (24.4)
Permanent visual loss, n (%)	16 (35.5)
Unilateral visual loss, n (%)	10 (22.2)
Bilateral visual loss, n (%)	6 (13.3)
Polymyalgia rheumatica, n (%)	16 (35.6)
Extracranial vessel involvement, n (%)	8 (17.8)
Neurologic manifestations, n (%)	3 (6.7)

n - number of patients.

Table 2 - Comparison between patients with biopsy-proven GCA and those classified according the ACR criteria for GCA.

Variables	Biopsy-proven GCA (N = 16)	GCA based on ACR criteria (N = 29)	*p*-value
Median age at study, years	80.5 (56-87)	78.0 (58-86)	0.141
Females, n (%)	12 (75.0)	17 (58.6)	0.221
Caucasians, n (%)	14 (87.5)	25 (86.2)	0.642
Temporal headache, n (%)	13 (81.3)	24 (82.8)	0.600
Occipital headache, n (%)	0 (0.0)	6 (20.7)	0.058
Jaw claudication, n (%)	7 (43.8)	15 (51.7)	0.608
Polymyalgia rheumatic, n (%)	3 (18.8)	13 (44.8)	0.075
Systemic manifestations, n (%)	7 (43.8)	13 (44.8)	0.944
Neuro-ophthalmic manifestations, n (%)	13 (81.3)	18 (62.1)	0.160
Extracranial vessel involvement, n (%)	3 (18.8)	5 (17.2)	0.600
Neurological manifestations, n (%)	2 (12.5)	1 (3.4)	0.285
Mean ESR at diagnosis, mm/hour	90.1 ± 41.7	71.3 ± 25.7	0.075

Numerical data are presented as the medians and ranges or as the means ± standard deviations; ACR – American College of Rheumatology; ESR – erythrocyte sedimentation rate; GCA – giant cell arteritis; n – number of patients.

was involved in one patient (2.2%). The dissection of the thoracic aorta was observed in only one patient (2.2%) with an aortic aneurysm. Stenosis of extra-cranial arteries was found in five (11.1%) patients with GCA. Subclavian arteries were involved in four cases (8.8%), common carotid arteries were involved in two (4.4%), and the common iliac arteries and superior mesenteric artery were involved in one patient each (2.2%). No patients developed cervical artery stenosis. Peripheral neuropathy was the only neurologic manifestation observed, and no patients developed stroke during the follow-up period. The mean ESR value at disease onset was 78.4 ± 33.4 mm/1st hour.

Therapy

All patients were treated with oral corticosteroids at disease onset and during any relapses; intravenous methylprednisolone was administered to 23 (51.1%) patients. Oral weekly methotrexate was prescribed to 21 (46.7%) patients at a median dose of 15 mg (95% CI: 14.8–18.5). An alternative immunosuppressive agent was prescribed to four GCA patients (8.8%); two patients took oral cyclophosphamide, and two took azathioprine. Aspirin was prescribed to 32 (71.1%) and statins to 16 (35.6%) patients.

Relapses

Most GCA patients had a monophasic disease course, and relapses were observed in 13 (28.9%) patients. The median number of relapses was 1.0 (95% CI: 0.99–1.93). PMR was the most common reactivation form (occurring in six relapses). AION occurred in five relapses, new onset of temporal headache occurred in three, extra-cranial vasculitis occurred in two, and polyarthritis occurred in one. Jaw claudication, PMR and the involvement of large vessels were the GCA manifestations most commonly found during disease course among relapsing patients compared with patients with monophasic disease. Patients with monophasic disease used aspirin more frequently than relapsing patients, and no significant relapse differences were found in GCA patients treated with methylprednisolone intravenous pulse, methotrexate or statins (Table 3).

Univariate analysis showed that aspirin had a protective effect against relapses (OR 0.19; 95% CI: 0.04–0.80; $p = 0.024$). A higher risk for relapse was found in GCA patients who presented PMR (OR 8.03; 95% CI: 1.89–34.10; $p = 0.005$), jaw claudication (OR 10.5; 95% CI: 1.96–55.99; $p = 0.006$) and the involvement of extra-cranial arteries (OR 6.04; 95% CI: 1.18–30.87; $p = 0.031$). After adjusting for age, gender and ethnicity in a multivariate model, the beneficial effects of aspirin use to prevent relapses (OR 0.02; 95% CI: 0.001–0.60; $p = 0.023$), as well as the higher risk for relapses associated with jaw claudication (OR 21.86; 95% CI: 1.32–360.28; $p = 0.031$) and the involvement of extra-cranial arteries (OR 45.91; 95% CI: 1.40–1503.54; $p = 0.032$), remained significant.

Outcomes

During follow-up, 41 (91.1%) GCA patients developed at least one complication related to long-term corticosteroid use, including systemic hypertension (66.7%), dyslipidemia (37.8%), osteoporosis (37.8%), diabetes (33.3%), cataracts (20.0%) or glaucoma (8.9%). Coronary heart disease was observed in only two patients (4.4%) during the follow-up period. Four GCA patients (8.9%) developed cancer during the study period; lymphoma was diagnosed in two patients, and skin basal cell carcinoma and breast cancer were diagnosed in one patient each. Four GCA patients (8.9%) died during the study, including three from neoplasia (two with lymphoma and one with breast cancer) and one with sepsis due to severe pneumonia.

Comparisons between genders

Female GCA patients had a higher prevalence of PMR, systemic manifestations and jaw claudication than male patients. Moreover, they developed more osteoporosis and dyslipidemia during the course of the disease as complications due to chronic steroid therapy. Permanent visual loss was significantly more prevalent in men with GCA than women (Table 4).

DISCUSSION

To the best of our knowledge, this is the first study addressing the features of Brazilian GCA patients. Jaw claudication, PMR and extra-cranial vessel involvement were more commonly found in patients with relapsing disease. Furthermore, female patients had a higher prevalence of PMR, systemic manifestations and jaw claudication than men, while the latter developed permanent visual loss more frequently. Finally, antiplatelet therapy was associated with a lower relapse rate. The purpose of this study was to describe GCA features in a country where GCA is uncommon.

Table 3 - Comparison between monophasic and relapsing patients with giant cell arteritis.

Variables	Relapsing patients (n = 13)	Non-relapsing patients (n = 32)	*p*-value
Median age at onset, years	70.0 (54-80)	75.5 (55-82)	0.065
Females, n (%)	11 (84.6)	18 (56.3)	0.072
Non-Caucasians, n (%)	3 (21.1)	3 (9.4)	0.220
Polymyalgia rheumatica, n (%)	9 (69.2)	7 (21.9)	0.003*
Systemic manifestations, n (%)	7 (53.8)	13 (40.6)	0.419
Temporal headache, n (%)	11 (84.6)	26 (81.3)	0.789
Occipital headache, n (%)	2 (15.4)	4 (12.5)	0.796
Jaw claudication, n (%)	11 (84.6)	11 (34.4)	0.002*
Neuro-ophthalmic manifestations, n (%)	7 (53.8)	24 (75.0)	0.165
Permanent visual loss, n (%)	3 (23.1)	13 (40.6)	0.265
Extra-cranial vessel involvement, n (%)	5 (38.5)	3 (9.4)	0.021
Mean ESR at diagnosis, mm/hour	69.3 ± 44.6	82.7 ± 27.2	0.346
Methotrexate use, n (%)	8 (61.5)	13 (40.6)	0.202
Intravenous pulse with MP, n (%)	5 (38.5)	18 (56.3)	0.279
Statins use, n (%)	6 (46.2)	10 (31.3)	0.344
Aspirin use, n (%)	6 (46.2)	26 (81.3)	0.019
Deaths, n (%)	2 (15.4)	2 (6.3)	0.329

Numerical data are presented as the medians and ranges or as the means ± standard deviations; ESR - erythrocyte sedimentation rate; n - number of patients; MP – methylprednisolone.

The median age of disease onset among Brazilian GCA patients was 73.0 years, which falls within the previously described peak of incidence between 70 and 80 years of age (4,11). The age of disease onset of approximately half of our patients was clustered between 70 and 79 years. However, we found no increase in GCA incidence rate in patients between 80 and 89 years of age, and no cases of GCA were diagnosed after the age of 90 years. This differs from the literature, in which the risk of developing GCA increases with advancing age and the incidence of GCA is 20-fold higher among individuals older than 90 years than in those between 50 and 60 years (12).

Similarly to other studies, Brazilian GCA patients were predominantly female (1,2). The reason for this is not completely understood; sex-based hormonal differences could be a possible explanation because androgens seem to play a protective role against autoimmunity and men are exposed to higher androgen levels than women throughout their lives. Due to the post-menopausal onset of GCA, estrogens are less likely to be involved in the pathogenesis (13,14). No significant differences in GCA manifestations between genders have been found in large series evaluating patients with GCA; only an increased prevalence of headache in women was observed in the study performed by Machado et al. (15). However, the higher prevalence of PMR and systemic manifestations among female patients and the higher prevalence of permanent visual loss among the men in our study are in accordance with the results observed in studies that specifically addressed sex differences in GCA (13,16,17).

The prevalences of most GCA manifestations in Brazilian patients are similar to those described by other studies; the

Table 4 - Comparison between males and females with giant cell arteritis.

Variables	Females (n = 29)	Males (n = 16)	*p*-value
Mean age at onset, years	70.3 ± 6.5	72.9 ± 9.1	0.323
Non-Caucasians, n (%)	6 (20.7)	0 (0.0)	0.051
Polymyalgia rheumatica, n (%)	14 (48.3)	2 (12.5)	0.016*
Systemic manifestations, n (%)	17 (58.6)	3 (18.8)	0.010*
Temporal headache, n (%)	26 (89.7)	11 (68.8)	0.079
Occipital headache, n (%)	4 (13.8)	2 (12.5)	0.903
Jaw claudication, n (%)	20 (69.0)	2 (12.5)	<0.001
Neuro-ophthalmic manifestations, n (%)	19 (65.5)	12 (75.0)	0.511
Permanent visual loss, n (%)	6 (20.7)	10 (62.5)	0.005*
Extra-cranial vessel involvement, n (%)	5 (17.2)	3 (18.8)	0.899
Mean ESR at diagnosis, mm/hour	80.3 ± 34.4	74.2 ± 31.8	0.579
Complications due to steroid therapy, n (%)	28 (96.6)	13 (81.3)	0.084
Systemic hypertension, n (%)	22 (75.9)	8 (50.0)	0.078
Diabetes, n (%)	12 (41.4)	3 (18.8)	0.123
Dyslipidemia, n (%)	15 (51.7)	2 (12.5)	0.009
Osteoporosis, n (%)	15 (51.7)	2 (12.5)	0.009
Cataracts, n (%)	4 (13.8)	5 (31.3)	0.161
Glaucoma, n (%)	2 (6.9)	2 (12.5)	0.527
Coronary heart disease, n (%)	2 (6.9)	0 (0.0)	0.283
Cancer, n (%)	3 (10.3)	1 (6.3)	0.644
Deaths, n (%)	3 (10.3)	1 (6.3)	0.644

Numerical data are presented as the medians and ranges or as the means ± standard deviations; ESR - erythrocyte sedimentation rate; n - number of patients.

only exception is the lower prevalence of systemic manifestations, such as fever, anorexia and weight loss, in Brazilian patients (1-3,6,15). Due to the retrospective nature of this study, systemic manifestations may have been undervalued and not indicated in the medical records. The high prevalence of neuro-ophthalmic manifestations in this study may be due to referral bias because most GCA patients were referred by ophthalmologists (i.e., all 31 patients with neuro-ophthalmic manifestations). Thus, the high rate of permanent visual loss may reflect the higher prevalence of visual symptoms, in addition to reflecting the delay in recognition of disease features and the low threshold for the diagnosis of GCA due to its rarity in Brazil. Salvarani et al. (18) showed that most cases of permanent visual loss develop prior to the start of corticosteroid therapy. AION was the leading neuro-ophthalmic manifestation in our patients, and it has been reported in approximately 90% of patients with visual symptoms due to GCA (18,19). Amaurosis fugax is recognized as a risk factor for the cranial ischemic complications of GCA (20), and it preceded AION in one-third of our cases.

The prevalence of aortic aneurysms in our patients was lower than the 9.5–18.0% previously described (21,22). Despite the low prevalence of aortic aneurysms in this study, one patient developed an aneurysm dissection in the thoracic aorta, and this life-threatening complication reaffirms the importance of evaluating GCA patients for large vessel involvement. The prevalence of arterial stenosis in our study is similar to the 13–14% previously described, and it involved mainly subclavian and common carotid arteries (22,23).

In this study, corticosteroids were the most prescribed therapy for active GCA. Although a small trial that included biopsy-proven GCA patients found that intravenous methylprednisolone led to a higher rate of sustained remission, a lower daily dose of prednisone and lower cumulative dose of glucocorticoid, in this study, it was reserved mostly for patients with neuro-ophthalmic manifestations (24). Methotrexate was prescribed to our patients after the first relapse based on a meta-analysis that showed the benefit of methotrexate in preventing relapses and reducing exposure to corticosteroids (25).

The frequency of disease relapses in our study was slightly lower than the 30–50% described by other studies (26-29). Although PMR and temporal headache are common features observed in relapsing GCA (26), we found an unexpectedly high frequency of AION among relapsing patients. We also found higher prevalences of PMR, jaw claudication and extra-cranial vessel involvement as GCA manifestations during the course of the disease in relapsing patients. However, in a study that specifically addressed relapses in patients with GCA, no significant differences were found in the disease manifestations of relapsing and non-relapsing patients (26).

Two retrospective cohort studies (30,31) found that antiplatelet therapy with low-dose aspirin reduces cranial ischemic complications of GCA, including visual loss and cerebrovascular accidents. Most of our patients were treated with low-dose aspirin, and we observed a protective effect of aspirin on disease relapses. We speculate that the prevention of cranial complications may have accounted for the lower rate of relapses in patients treated with aspirin. Narváez et al. (32) did not find any effect of aspirin on either the prevention of cranial ischemic complications or GCA relapse rates.

Limitations of this study include its retrospective design, the relatively small number of patients and the fact that it was based on referral centers. Most limitations may be explained by the rarity of GCA in Brazil. In this setting, essentially all recognized patients with GCA are referred to tertiary centers for follow-up and management. Referral delays and previous treatment with high-dose corticosteroids are some reasons for the relatively low frequency of temporal artery biopsy (40%) in GCA patients observed in this study. Another limitation of this study is the underestimation of extra-cranial arterial involvement in GCA, as its screening in our patients relied only on signs and symptoms of vascular manifestations and finding vascular abnormalities by chance on imaging studies performed for other purposes. It is now well known that extra-vascular involvement can occur asymptomatically, even at the time of GCA diagnosis (33).

In conclusion, GCA in Brazil is mostly found among female Caucasians, and the majority of clinical features are similar to those found in other studies, except for the low frequency of systemic symptoms and high prevalence of neuro-ophthalmic manifestations, including permanent blindness. A significant protective effect of aspirin against disease relapses was observed.

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AUTHOR CONTRIBUTIONS

Souza AW contributed to the study design, performed the statistical analysis and wrote the manuscript. Okamoto KY contributed to the study design and participated in the collection of data and manuscript revision. Abrantes F, Schau B and Bacchiega AB participated in the collection of data and revised the manuscript. Shinjo SK contributed to the study design, participated in the collection of data and revised the manuscript.

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