Strokes at Time of Disease Diagnosis in a Series of 287 Patients With Biopsy-Proven Giant Cell Arteritis

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Abstract: Patients with giant cell arteritis (GCA) generally present with cranial ischemic manifestations that are directly related to vascular involvement. They may also experience strokes in the territory of the carotid or the vertebrobasilar artery. We conducted the current study to assess the frequency and predictors of strokes in general, and of vertebrobasilar stroke in particular, at the time of diagnosis in a series of 287 consecutive patients with biopsy-proven GCA diagnosed over a 27-year period at the single hospital for a well-defined population of northwestern Spain.

During the study period, 8 (2.8%) patients had strokes (1 in the carotid and 7 in the vertebrobasilar territory) between the onset of symptoms of the disease and 4 weeks after the onset of corticosteroid therapy. Six of the 7 patients with vertebrobasilar stroke were men. In most cases the vertebrobasilar stroke occurred after the onset of corticosteroid therapy. Smoking history was more common among patients with vertebrobasilar stroke ($p = 0.01$). Patients with vertebrobasilar stroke more commonly had permanent visual loss due to arteritic involvement of ophthalmic branches derived from the internal carotid (3/7; 42.9%) than the rest of GCA patients (33/280; 11.8%) ($p = 0.05$). Patients with strokes had higher hemoglobin values (13.2 ± 1.5 g/dL) than patients without (11.7 ± 1.6 g/dL) ($p = 0.009$). Moreover, only 1 (14.3%) of the 7 patients with vertebrobasilar stroke had anemia compared to 157 (56.1%) of the remaining 280 patients ($p = 0.05$). The best predictors of stroke were permanent visual loss (odds ratio [OR], 5.42) and arterial hypertension (OR, 5.06). In contrast, women (OR, 0.10) and patients with anemia at the time of disease diagnosis (OR, 0.11) had a significantly reduced risk of suffering strokes. Smoking history was the best positive predictor of vertebrobasilar stroke (OR, 5.22). In contrast, a reduced risk of suffering vertebrobasilar strokes was found in individuals who had anemia at the time of GCA diagnosis (OR, 0.13).

Results of the current study show an increased risk of strokes, in the vertebrobasilar territory in particular, at the time of GCA diagnosis. Patients with biopsy-proven GCA and traditional cardiovascular risk factors or permanent visual loss have an increased risk of suffering strokes. Results also suggest a potential protective role of anemia against the development of these cerebrovascular complications.

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Abbreviations: CI = confidence intervals, CT = computed tomography, ESR = erythrocyte sedimentation rate, GCA = giant cell arteritis, IR = incidence ratio, MRI = magnetic resonance imaging, OR = odds ratio, PMR = polymyalgia rheumatica, RD = risk difference, TIA = transient ischemic attack, VEGF = vascular endothelial growth factor.

INTRODUCTION

Giant cell, temporal, arteritis (GCA), also called granulomatous arteritis, is a large and medium-sized blood vessel systemic vasculitis characterized by the granulomatous involvement of the aorta and its major branches with predilection for the extracranial branches of the carotid artery.[33,42] GCA is exceptional in individuals aged younger than 50 years. However, the incidence of this vasculitis increases with age and peaks in white individuals aged older than 70 years.[27] Due to the progressive aging of the population in Western countries along with well-characterized genetic components,[12] GCA has became the most common type of systemic vasculitis in North American and European people over the age of 50 years.[18]

Forty percent to 60% of the patients with GCA have clinical manifestations of polymyalgia rheumatica (PMR).[13,31,42] It may also be the presenting feature in some patients who later develop typical cranial ischemic manifestations of GCA.[10,13] However, the typical features of GCA are the result of the vasculitic involvement of arteries derived from the aorta. Classically, GCA patients present with cranial ischemic manifestations.[33,42] Headache is the most common feature, observed in more than two-thirds of patients.[31,33] This feature as well as other common manifestations such as scalp tenderness or jaw claudication is due to the arteritic involvement of branches derived from the external carotid.[13]

Visual manifestations constitute the most common severe complications of GCA.[1] They occur in about 30% of patients, leading to permanent loss of vision in 15%.[1,20] In most cases visual symptoms are due to anterior ischemic optic neuropathy, frequently preceded by amaurosis fugax. More rarely, visual loss is caused by central retinal artery occlusion. These ocular manifestations are caused by the vasculitic involvement of branches derived from the internal carotid artery.[1,20] Less commonly, patients may present with claudication of the extremities, in particular of the arms, due to large-artery involvement of branches of the aortic arch, mainly the subclavian and the axillary arteries.[42] Aortic aneurysmal disease may also be observed in patients with GCA, in particular during the extended follow-up of these patients.[21,38]

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GCA patients may experience strokes in the territory of the carotid or vertebrobasilar artery.[6,37,40] These are considered uncommon complications of GCA.[42] Strokes are typically observed in the period of clinically active disease, between the onset of symptoms of GCA until the first month after the initiation of steroid therapy.[15,39] Although long-term survival studies have shown no overall excess mortality in GCA patients compared to control populations,[14,30,35] strokes, particularly due to involvement of the vertebrobasilar territory, were reported to be a significant cause of early mortality and morbidity, at the time of disease diagnosis, in patients with this vasculitis.[29,37] Vertebrobasilar strokes are more common in GCA patients with active disease than in the general population of the same age.[6,42] However, unlike aneurysmal disease, strokes in the vertebrobasilar territory do not appear to be late complications of GCA.[29,39]

Although cases of strokes in patients with GCA have been extensively reported, information on this issue based on large series of individuals in population-based studies is limited. This information is of major importance to establish the actual incidence of strokes in patients with biopsy-proven GCA. Moreover, little is known about possible differences between GCA patients who have strokes and those who do not. Similarly, information about predictors of strokes in general, and of vertebrobasilar stroke specifically, in the context of GCA is scarce.

In an earlier study by our group that encompassed 210 biopsy-proven GCA patients diagnosed in Lugo, Spain, between 1981 and 2001, we analyzed the frequency and type of strokes in GCA patients from our region that occurred before the GCA diagnosis, at the time of disease diagnosis, and afterwards, in the extended follow-up of these patients. We observed that the incidence of strokes occurring between the onset of GCA symptoms and 1 month after the start of corticosteroid therapy was increased compared with the incidence in the other time periods.[39] Moreover, vertebrobasilar strokes were more common than carotid strokes in that period of time close to the GCA diagnosis: 3 of the 4 patients from that study who experienced strokes at the time of disease diagnosis had vertebrobasilar strokes. However, it was not the case for strokes occurring before the onset of GCA symptoms or from 1 month after the onset of corticosteroid treatment onward—those involved the carotid territory more commonly. Moreover, since 2001 we have seen more patients with biopsy-proven GCA who suffered vertebrobasilar strokes in the period between the onset of GCA symptoms and 1 month after the beginning of steroid therapy.

Considering these issues, we conducted the present study to investigate further the incidence of strokes in patients with GCA at the time of disease diagnosis. For this purpose we assessed a large series of patients who had biopsy-proven GCA over a 27-year period in a defined population.

PATIENTS AND METHODS

We performed a retrospective review of the case records of all patients diagnosed with biopsy-proven GCA at the Department of Medicine of the Hospital Xeral-Calde (Lugo, Spain) between January 1, 1981, and April 30, 2008. This hospital is the reference center for a mixed rural and urban population of almost a quarter of a million people. The characteristics of this white population have been previously described.[17,25]

The temporal artery biopsy procedure in Lugo patients has been reported elsewhere.[20,23] Biopsies were routinely performed in all patients with clinical manifestations of GCA.[11,22] The side with predominant symptoms and signs was selected for biopsy. Biopsies were also considered for patients with clinically isolated PMR, with no vascular manifestation of GCA, if the patient had constitutional syndrome (asthenia, anorexia, and weight loss of at least 4 kg) and/or had an erythrocyte sedimentation rate (ESR) by Westergren method greater than 80 mm/1st hour.[22,23] Patients included in this study were considered to have biopsy-proven GCA when the temporal artery biopsy showed a compatible pathology report describing the characteristic mononuclear cell infiltration of the arterial wall, with or without the presence of granulomas and/or multinucleated giant cells.[19]

Exposures

Definitions of GCA manifestations in the Lugo population have also been previously described.[13,26] Clinical manifestations were considered within the category of presenting features of the disease if they occurred within a period of time between the onset of GCA symptoms and 4 weeks after the start of corticosteroid therapy (initial dose 40–60 mg prednisone/day for 3–4 weeks or intravenous methylprednisolone pulse therapy [1 g daily for 3 d] followed by 60 mg prednisone/day for 3–4 weeks in most patients who had visual manifestations or other severe ischemic manifestations such as limb claudication or stroke).[13]

Outcomes

All patients in whom stroke was diagnosed had lesions on computed tomography (CT) and/or magnetic resonance imaging (MRI) scans that were read by a neuroradiologist and correlated clinically by a neurologist. As a result, patients with stroke involving the vertebrobasilar territory had to present clinical features such a homonymous hemianopsia, cortical blindness, ataxia, dysarthria, diplopia, dysphagia, hemiparesis, or hemisensory loss contralateral to the cranial nerves palsy. In contrast, besides having a lesion located in regions of the carotid territory, patients with GCA in whom stroke in the carotid territory was diagnosed had to present typical features such as homonymous hemi- or quadrantanopia, dysphasia, hemiparesis/hemiplegia, hemisensory loss/disturbance or astereognosis, agraphesthesia, impaired 2-point discrimination, sensory and visual inattention, left-right dissociation, and acalculia. Moreover, at the time the study, in all cases a retrospective review of the lesions on CT and MRI scans was performed by a neurologist (RPR) that confirmed the location of the brain lesion. As a result, strokes were finally classified according to the location of the lesion.

For the purpose of the current study, patients who had brief episodes of isolated vertigo or dysarthria were excluded. Also, patients with transient neurologic disturbances, transient ischemic attacks (TIAs), including those involving the carotid or the vertebrobasilar territories, were excluded.

Definitions of hypercholesterolemia, hypertension, and diabetes mellitus were the same as those used to establish the influence of traditional cardiovascular risk factors in the clinical spectrum of GCA in northwestern Spain.[26] With regard to smoking, we established 2 categories: current smokers, which comprised patients who smoked at the time of the diagnosis of GCA or who had smoked within the 10 years before the onset of GCA symptoms, and the remaining patients (former or never smokers), who had never smoked or had stopped smoking at least 10 years before the onset of symptoms of GCA.[28]

Data Collection

We analyzed the demographic and clinical data at the time of diagnosis or within the 4 weeks after the onset of treatment for all the patients with biopsy-proven GCA.

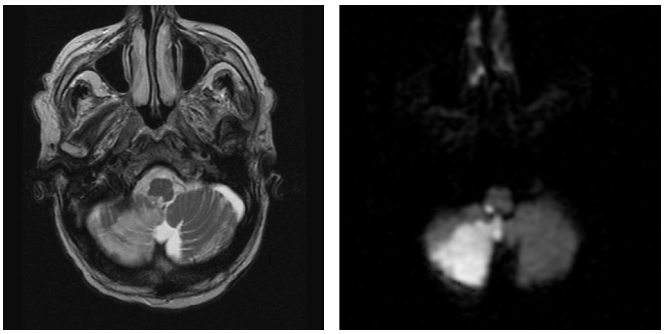

FIGURE 1. Stroke in the territory of the right posterior-inferior cerebellar artery in an 85-year-old man with biopsy-proven GCA (T2- and diffusion-weighted MRI sequences).

Besides age at disease diagnosis, sex, and delay to disease diagnosis from the onset of symptoms, we assessed history of hypertension, hypercholesterolemia, smoking (current smoking), diabetes mellitus, and atrial fibrillation at the time of diagnosis of GCA, and antiaggregation or anticoagulation before the diagnosis of GCA. Moreover, data on the following clinical items were analyzed: constitutional syndrome, fever (temperature >38°C), headache, abnormal temporal artery on physical examination, scalp tenderness, dysphagia, jaw claudication, PMR, visual ischemic manifestations, strokes (involving the carotid or the vertebrobasilar territory), and peripheral arteriopathy of recent onset. Also, ESR, hemoglobin value, platelet count, white blood cell count, albumin, and alkaline phosphatase data on admission were assessed for all patients.

Statistical Analysis

Continuous data were described as mean and standard deviation (mean ± SD), and categorical variables as percentage; 95% confidence intervals (CI) for risk differences were estimated using the Cornfield method. The Fisher exact test was used to analyze categorical data. For continuous variables, a statistical comparison was performed with the Mann-Whitney U test.

We reported previously that the presence of atherosclerosis risk factors at the time of diagnosis of GCA, in particular the presence of hypertension, may influence the development of severe ischemic manifestations of the disease.[26] Because of that, to obtain a predictive model for strokes in general or more specifically for vertebrobasilar stroke at the time of GCA diagnosis, we performed a forward stepwise logistic regression with an entry p value of 0.20; final models were validated via jackknifing. Results were shown as odds ratios (ORs) and 95% CI. Statistical significance was defined as $p \leq 0.05$. Calculations were performed with the statistical package Stata 10/SE (Stata Corporation, College Station, TX).

RESULTS

Between January 1, 1981, and April 30, 2008, biopsy-proven GCA was diagnosed in 287 consecutive patients in Lugo. All the patients met the 1990 American College of Rheumatology criteria for the classification of GCA.[32]

Strokes in Patients With Biopsy-Proven GCA

Eight (2.8%) of the 287 GCA patients included in the current study experienced strokes between the onset of symptoms of the disease and 4 weeks after the beginning of corticosteroid therapy. Seven (87.5%) of these 8 patients had a vertebrobasilar stroke. Six of the 7 patients with vertebrobasilar strokes were men. In 5 of them the stroke occurred once corticosteroid therapy for the treatment of GCA had been initiated (3, 4, 7, 10 days, and 4 weeks, respectively, after the onset of 40–60 mg prednisone/d). MRI results of 2 representative cases are shown in Figures 1 and 2. Another man presented at the emergency department because of vertigo and headache. He had been diagnosed with PMR in another center 1 year before. However, he had maintained a dosage of 10 mg prednisone/day since that diagnosis. The neurologic examination showed gait unsteadiness and ataxia. An angio-MRI scan showed bilateral vertebral artery occlusion. Finally, a woman who was being treated with acenocoumarin due to atrial fibrillation suffered an occipital infarction 3 weeks before the diagnosis of GCA.

A stroke involving the carotid territory was observed in only 1 (0.4%) of the 287 patients with biopsy-proven GCA. It occurred before the onset of corticosteroid therapy.

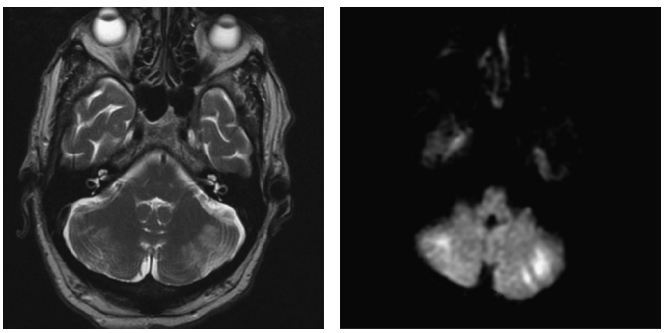

FIGURE 2. Bilateral cerebellar stroke in a 79-year-old man with biopsy-proven GCA (T2- and diffusion-weighted MRI sequences).

TABLE 1. Epidemiologic Differences Between Biopsy-Proven GCA Patients With Strokes Involving the Carotid or Vertebrobasilar Territory or Patients Without Strokes at Time of Disease Diagnosis

	With No. (%)	Without No. (%)	p Value
No. of patients	8 (2.8)	279 (97.2)	
Delay to diagnosis*, wk	11.5 ± 16.7	9.8 ± 10.4	0.60
Age*, yr	74.4 ± 9.0	75.3 ± 6.8	0.98
Women	1 (12.5)	154 (55.2)	0.03
Hypertension	5 (62.5)	107 (39.2)	0.27
Hypercholesterolemia	3 (37.5)	46 (16.7)	0.14
Diabetes mellitus	1 (12.5)	24 (8.7)	0.53
Current smoker	4 (50.0)	41 (14.9)	0.02
Antiaggregation or anticoagulation before the diagnosis of GCA	1 (12.5)	28 (10.0)	0.58
Atrial fibrillation	1 (12.5)	21 (7.5)	0.48

*Mean ± SD.

When comparing our data with those from a study that assessed the incidence of stroke in the Spanish population,[2] we found an increased standardized incidence ratio (IR) in men (IR, 2.20; 95% CI, 0.93–5.20) but a decreased standardized IR in women (IR, 0.53; 95% CI, 0.07–3.77). However, the relatively small number of patients with stroke in our sample prevented us from extracting conclusions about the overall effect of GCA on stroke risk at the time of diagnosis of this vasculitis.

Epidemiologic Differences Between GCA Patients With or Without Strokes

No differences in age at the time of diagnosis of GCA or in the delay to disease diagnosis were observed between patients who experienced strokes and the remaining GCA patients (Table 1). However, the frequency of strokes was significantly reduced in women compared to men (risk difference [RD], 4.66%; 95% CI, 0.63%–8.68%; p = 0.03). This difference by sex was also statistically significant when we specifically compared GCA patients with vertebrobasilar stroke with the rest of GCA patients (RD, 3.90%; 95% CI, 0.13%–7.67%; p = 0.05) (Table 2). Hypertension was more commonly found in the group of patients with strokes than in those without (62.5% vs. 39.2%, respectively) but the difference was not statistically significant (Table 1). However, smoking history was significantly more common among patients who developed strokes than those who did not (50.0% vs. 14.9%, respectively; p = 0.02).

Clinical Differences Between GCA Patients With or Without Strokes

Clinical differences between patients with GCA who experienced strokes in general or vertebrobasilar strokes in particular and the rest of patients with GCA are shown in Tables 3 and 4. Patients with vertebrobasilar strokes more commonly had permanent (irreversible) visual loss due to arteritic involvement of ophthalmic branches derived from the internal carotid (3/7; 42.9%) compared with the rest of GCA patients (33/280; 11.8%) (p = 0.05) (Table 4).

Laboratory Differences Between GCA Patients With or Without Strokes

Patients with strokes had lower ESR levels at the time of disease diagnosis compared with patients without strokes (81.6 ± 20.0 mm/1st h vs. 93.8 ± 22.7 mm/1st h, respectively), but the difference remained out of the range of significance (p = 0.10) (Table 5). Likewise, lower platelet counts were observed in patients with strokes in general or specifically in the subgroup of GCA patients who had vertebrobasilar strokes, but

TABLE 2. Epidemiologic Differences Between Biopsy-Proven GCA Patients With Vertebrobasilar Stroke or Without Vertebrobasilar Stroke at Time of Disease Diagnosis

	With No. (%)	Without No. (%)	p Value
No. of patients	7 (2.4)	280 (97.6)	
Delay to diagnosis*, wk	12.9 ± 17.6	9.77 ± 10.36	0.99
Age*, yr	73.9 ± 9.6	75.3 ± 6.8	0.84
Women	1 (14.29)	154 (55)	0.05
Hypertension	4 (57.14)	108 (39.42)	0.44
Hypercholesterolemia	2 (28.57)	47 (16.97)	0.35
Diabetes mellitus	0 (0)	25 (9.06)	1.00
Current smoker	4 (57.14)	41 (14.80)	0.01
Antiaggregation or anticoagulation before the diagnosis of GCA	1 (14.29)	28 (10)	0.53
Atrial fibrillation	1 (14.29)	21 (7.50)	0.43

*Mean ± SD.

TABLE 3. Clinical Differences Between Biopsy-Proven GCA Patients With or Without Strokes at Time of Disease Diagnosis

	With No. (%)	Without No. (%)	p Value
No. of patients	8 (2.8)	279 (97.2)	
Constitutional syndrome	4 (50.0)	168 (60.2)	0.72
Fever (temperature ≥38°C	0 (0)	32 (11.5)	0.60
Headache	5 (62.5)	238 (85.3)	0.11
Abnormal temporal artery on physical examination	6 (75.0)	197 (70.6)	1.00
Scalp tenderness	2 (25.0)	99 (35.5)	0.72
Dysphagia	0 (0)	13 (4.7)	1.00
Jaw claudication	2 (25.0)	113 (40.5)	0.48
Polymyalgia rheumatica	5 (62.5)	109 (39.1)	0.27
Visual ischemic manifestations	4 (50.0)	62 (22.2)	0.09
Transient visual loss (including amaurosis fugax)	2 (25.0)	34 (12.2)	0.26
Irreversible visual loss	3 (37.5)	33 (11.8)	0.07
Peripheral arteriopathy of recent onset	0 (0)	6 (2.2)	1.00

the difference was not statistically significant (Tables 5 and 6). More importantly, patients with strokes had higher hemoglobin values (13.2 ± 1.5 g/dL) than the GCA patients without strokes (11.7 ± 1.6 g/dL) (p = 0.009) (Table 5). This was also the case for those with vertebrobasilar stroke (Table 6). In this regard, only 1 (14.3%) of the 7 patients with vertebrobasilar stroke had hemoglobin values less than 12 g/dL compared with 157 (56.1%) of the 280 patients without stroke in the vertebrobasilar territory (p = 0.05) (Table 6).

Predictors of Strokes in General and of Vertebrobasilar Strokes Specifically in Patients With Biopsy-Proven GCA

A history of hypertension before the diagnosis of GCA (OR, 5.06; 95% CI, 1.02–25.12; p = 0.05) and the presence of permanent visual loss due to arteritic involvement of branches derived from the ophthalmic artery (OR, 5.42; 95% CI, 1.26–23.39; p = 0.02) were the best predictors of strokes in this series of biopsy-proven GCA patients (Table 7). However, in both cases the CIs were quite wide, limiting the ability to derive strong inference of these ORs. In contrast, women (OR, 0.10; 95% CI, 0.04–0.26; p < 0.001) and biopsy-proven GCA patients with anemia at the time of disease diagnosis (OR, 0.11; 95% CI, 0.04–0.32; p < 0.001) had a significantly reduced risk of suffering strokes.

Smoking at the time of GCA diagnosis or within the 10 years before the onset of GCA symptoms was the best predictor of vertebrobasilar stroke (OR, 5.22; 95% CI, 0.88–30.89; p = 0.07). In contrast, a reduced risk of suffering vertebrobasilar strokes was found in individuals who complained of headache at the time of GCA diagnosis (OR, 0.15; 95% CI, 0.02–0.99; p = 0.05). Moreover, as observed for the development of strokes in general, we also found a reduced risk of suffering vertebrobasilar strokes in individuals who had anemia, defined as a hemoglobin value less than 12 g/dL, at the time of GCA diagnosis (OR, 0.13; 95% CI, 0.04–0.47; p = 0.002) (Table 8).

DISCUSSION

To our knowledge, the current report is the largest population-based study assessing the frequency of strokes in general and vertebrobasilar stroke in particular at the time of disease diagnosis in patients with biopsy-proven GCA from

TABLE 4. Clinical Differences Between Biopsy-Proven GCA Patients With Vertebrobasilar Stroke or Without Vertebrobasilar Stroke at Time of Disease Diagnosis

	With No. (%)	Without No. (%)	p Value
No. of patients	7 (2.4)	280 (97.6)	
Constitutional syndrome	3 (42.9)	169 (60.4)	0.44
Fever (temperature ≥38°C	0 (0)	32 (11.4)	1.00
Headache	4 (57.1)	239 (85.4)	0.08
Abnormal temporal artery on physical examination	5 (71.4)	198 (70.7)	1.00
Scalp tenderness	2 (28.6)	99 (35.4)	1.00
Dysphagia	0 (0)	13 (4.6)	1.00
Jaw claudication	2 (28.6)	113 (40.4)	0.71
Polymyalgia rheumatica	4 (57.1)	110 (39.3)	0.44
Visual ischemic manifestations	4 (57.1)	62 (22.1)	0.05
Transient visual loss (including amaurosis fugax)	2 (28.6)	34 (12.1)	0.22
Irreversible visual loss	3 (42.9)	33 (11.8)	0.05
Peripheral arteriopathy of recent onset	0 (0)	6 (2.1)	1.00

TABLE 5. Laboratory Differences Between Biopsy-Proven GCA Patients With or Without Strokes at Time of Disease Diagnosis

	With No. (%)	Without No. (%)	p Value
No. of patients	8 (2.8)	279 (97.2)	
ESR*, mm/1st h	81.6 ± 20.0	93.8 ± 22.7	0.10
ESR levels			0.21
ESR <70 mm/1st h	3 (37.5)	39 (14.0)	
ESR 70–100 mm/1st h	3 (37.5)	123 (44.1)	
ESR >100 mm/1st h	2 (25.0)	117 (42.0)	
Hemoglobin*, g/dL	13.2 ± 1.5	11.7 ± 1.6	0.009
Anemia (hemoglobin <12 g/dL)	1 (12.5)	157 (56.3)	0.03
Platelet count* x 10^3 cells/mm^3	350 ± 139	404 ± 131	0.18
Thrombocytosis (>400,000/mm^3)	2 (25.0)	138 (49.5)	0.28
WBC count*/mm^3	9375 ± 2574	9552 ± 2919	0.89
Leukocytosis (WBC >11,000/mm^3)	2 (25.0)	77 (27.6)	1.00
Albumin*, g/dL	3.16 ± 0.61	3.3 ± 0.6	0.38
Hypoalbuminemia (<3 g/dL)	1 (12.5)	62 (22.8)	1.00
Raised ALP	2 (25.0)	64 (23.0)	1.00

Abbreviations: ALP, alkaline phosphatase; ESR, erythrocyte sedimentation rate; WBC, white blood cell count.
*Mean ± SD.

southern Europe. This study also establishes the best set of predictors for these neurologic complications in patients with GCA.

Arteritic involvement of the internal carotid system, distinct from its ophthalmic branches, and the vertebrobasilar arterial system has been reported in patients with GCA.[6,39] However, the actual frequency of this complication needs to be clarified by the assessment of large series of patients with biopsy-proven GCA included in population-based studies.

In the current series, strokes occurred in 2.8% of the 287 patients at the time of GCA diagnosis. As previously reported,[40] most patients who experienced strokes (7 of 8) had involvement of the vertebrobasilar territory. Mayo Clinic investigators Caselli et al[5] reported cerebrovascular complications (TIA or strokes) in 12 (7.2%) of 166 patients with biopsy-proven GCA. They found a predominance of these complications involving the carotid territory: only 5 of the 12 patients had cerebrovascular events involving the vertebrobasilar territory (2 strokes).[5] However, a careful analysis of these data shows that only 4 strokes occurred in the period of time ranging between 27 days before and 33 days after a temporal artery biopsy was performed.[5] In this regard, strokes involving the vertebrobasilar territory occurred in patients 2 days before and 11 days after undergoing the temporal artery biopsy.[5] Thus, the percentage of strokes in the period between the onset of GCA symptoms and 1 month after the diagnosis was 2.4%, which is remarkably similar to that observed in our series. More recently, Salvarani et al[43]

TABLE 6. Laboratory Differences Between Biopsy-Proven GCA Patients With Vertebrobasilar Stroke or Without Vertebrobasilar Stroke at Time of Disease Diagnosis

	With No. (%)	Without No. (%)	p Value
No. of patients	7 (2.4)	280 (97.6)	
ESR*, mm/1st h	84.0 ± 20.4	93.7 ± 22.7	0.22
ESR levels			0.51
ESR <70 mm/1st h	2 (28.6)	40 (14.3)	
ESR 70–100 mm/1st h	3 (42.9)	123 (43.9)	
ESR >100 mm/1st h	2 (28.6)	117 (41.8)	
Hemoglobin*, g/dL	13.1 ± 1.64	11.7 ± 1.6	0.02
Anemia (hemoglobin <12 g/dL)	1 (14.3)	157 (56.1)	0.05
Platelet count* x 10^3 cells/mm^3	350 ± 150	404 ± 131	0.21
Thrombocytosis (>400,000/mm^3)	2 (28.6)	138 (49.3)	0.45
WBC count*/mm^3	9400 ± 2779	9551 ± 2914	0.92
Leukocytosis (WBC >11,000/mm^3)	2 (28.6)	77 (27.5)	1.00
Albumin*, g/dL	3.16 ± 0.61	3.33 ± 0.55	0.38
Hypoalbuminemia (<3 g/dL)	1 (16.7)	62 (26.7)	1.00
Raised ALP	2 (28.6)	64 (22.9)	0.66

Abbreviations: See previous tables.
*Mean ± SD.

have reported the frequency of strokes at the time of diagnosis of GCA in patients from Reggio-Emilia, Italy. They described 5 (2.8%) patients who experienced strokes from a series of 180 patients with biopsy-proven GCA, all of them in the vertebrobasilar territory, between the onset of GCA symptoms and signs and 1 month after the onset of corticosteroid therapy.[43] It is noteworthy that the percentage of strokes observed at the time of GCA in Reggio-Emilia is exactly the same as that reported in our series. These findings support previous observations from a collaborative epidemiologic study aimed at establishing potential differences in the clinical spectrum of GCA in Lugo and Reggio-Emilia.[16] Although the incidence of biopsy-proven GCA in Lugo is higher than in Reggio-Emilia,[25,27] in that earlier study we observed that the clinical spectrum of GCA is similar in those regions of southern Europe.[16]

As in the current study, 2 of the 4 patients with stroke at the time of GCA diagnosis reported by Caselli et al[5] also had acute bilateral loss of vision. Also in keeping with our observations, Caselli et al emphasized that compared with cerebral infarctions due to all causes, the vertebrobasilar distribution of the damage was more common among GCA-related ischemic events.[5] In population-based epidemiologic studies of strokes and/or TIAs, the ratio of patients with carotid to patients with vertebrobasilar events is approximately 5:1.[44] This was also the ratio found in a previous study[39] by our group of 210 patients with biopsy-proven GCA diagnosed in Lugo between 1981 and 2001, when we analyzed the incidence of strokes in biopsy-proven GCA patients regardless of the temporal relationship between the diagnosis of GCA and the development of the strokes, instead of assessing the type and frequency of strokes at the time of GCA diagnosis. In that study, as expected in elderly people without GCA,[44] we found that patients with biopsy-proven GCA also suffered strokes in their extended follow-up, several months or years after the discontinuation of corticosteroid therapy, when the patients had no symptoms or clinical data that might suggest a relapse of the disease.[39] It is noteworthy that strokes occurring several months or years after the diagnosis of GCA involved more commonly the carotid territory.[39]

Taking into account these previous observations and the data derived from the current study encompassing a larger number of cases, we feel that the vasculitic process is by itself a major cause of vertebrobasilar stroke in patients with GCA. However, GCA is a disease of elderly people, and comorbid conditions such as hypertension or other traditional cardiovascular risk factors are not uncommon in this age-group. Moreover, in a previous study[26] we reported that the presence of traditional risk factors of atherosclerosis at the time of the diagnosis of GCA, in particular the presence of hypertension, significantly increased the risk of developing severe ischemic complications of the disease. Thus, in the current study, we also aimed to establish the potential implication of some classic risk factors of atherosclerosis in the development of strokes at the time of GCA diagnosis.

TABLE 7. Predictive Variables for Stroke Involving the Carotid or the Vertebrobasilar Territory*

Variable	OR (95% CI)†	p Value
Female sex (ref: male sex)	0.10 (0.04–0.26)	<0.001
Arterial hypertension	5.06 (1.02–25.12)	0.05
Permanent visual loss	5.42 (1.26–23.39)	0.02
Anemia	0.11 (0.04–0.32)	<0.001
Polymyalgia rheumatica	3.41 (0.92–12.72)	0.07

*Area under receiver operating characteristics (ROC) curve: 0.87.

†Adjusted OR obtained by multivariate logistic regression analysis; 95% CI and p values obtained via jackknife.

TABLE 8. Predictive Variables for Vertebrobasilar Stroke*

Variable	OR (95% CI)†	p Value
Headache	0.15 (0.02–0.99)	0.05
Anemia	0.13 (0.04–0.47)	0.002
Permanent visual loss	3.47 (0.64–18.90)	0.15
Current smoker	5.22 (0.88–30.89)	0.07

*Area under receiver operating characteristics (ROC) curve: 0.84.

†Adjusted OR (odds ratios) obtained by multivariate logistic regression analysis; 95% CI and p values obtained via jackknife.

We observed that a history of hypertension before the diagnosis of GCA was a strong predictor of strokes. Also, smoking at the time of GCA diagnosis or within the 10 years before the onset of GCA symptoms was a positive predictor of vertebrobasilar stroke. In contrast, female sex was associated with a decreased risk of strokes in patients with GCA. All these observations emphasize the role of traditional cardiovascular risk factors in the development of stroke in the setting of GCA.

Another point of interest that needed to be explored was the potential influence of both clinical features and laboratory markers of the GCA in the development of strokes. We observed a significantly increased frequency of permanent visual loss among the group of patients with GCA who suffered strokes. In these cases the cerebrovascular events occurred shortly after the ocular symptoms. Moreover, we found that patients with strokes, in particular those with vertebrobasilar strokes, had higher hemoglobin values than the patients with GCA without strokes at the time of disease diagnosis. Therefore, the presence of permanent visual loss was a positive predictor of strokes, while anemia at the time of disease diagnosis was associated with protection against the development of these neurologic complications.

A possible explanation for the increased risk of strokes in patients who experienced permanent visual loss may be that patients with this irreversible visual complication may also have more severe vasculitic damage. However, the protective role of anemia against the development of strokes deserves further discussion. Normochromic-normocytic anemia as the result of a chronic inflammatory response is common in patients with GCA at the time of disease diagnosis.[3] We note that a negative association between a strong inflammatory response and the risk of developing cranial ischemic complications was reported by Cid et al.[7] In their study, which included patients from several centers from northeastern Spain, the authors found that the hemoglobin values were significantly increased in the subgroup of patients with irreversible cranial ischemic complications.[7] In accordance with these observations, anemia was also found to be a negative predictive factor for the development of visual ischemic complications in GCA patients from northwestern Spain.[20] More recently, a multivariate logistic regression analysis disclosed that a hemoglobin value less than 12 g/dL was the only routine laboratory marker associated with a negative predictive value for the development of any severe ischemic complications (this category included patients presenting at least 1 of the following manifestations: visual ischemic complications, jaw claudication, strokes or limb claudication of recent onset) in patients with biopsy-proven GCA from northwestern Spain.[24]

The data from the current study assessing specifically the role of anemia in the development of strokes confirm that hemoglobin values lower than 12 g/dL are associated with protection against the development of these cerebrovascular complications in general and vertebrobasilar stroke in particular at the time of GCA diagnosis.

Cid et al[8] proposed an elegant explanation for the protection against severe ischemic complication of GCA mediated by a severe inflammatory response. These authors examined the clinical relevance of neovascularization in a series of 31 patients with GCA. They found that patients without severe ischemic complications had significantly higher tissue angiogenesis scores than those with severe ischemic events. Angiogenesis was also significantly more pronounced in patients with a strong acute phase response compared with those with a weak systemic inflammatory response.[8] Based on these results, Cid et al[8] proposed that an inflammation-induced angiogenic activity may play a compensatory role for ischemia in patients with GCA.

To investigate this issue further, we studied the potential implication of functional vascular endothelial growth factor (VEGF) gene polymorphisms in the susceptibility to severe ischemic complications of GCA.[41] We found that the subgroup of patients with severe occlusive disease, which included patients with permanent visual loss, stroke, or occlusive disease in the upper extremities related to GCA, carried genotypes associated with lower circulating VEGF levels in vivo and a reduced VEGF transcription.[41] All this evidence suggests that inflammation-induced angiogenic activity may counteract the development of severe ischemic complications in general and specifically of strokes in GCA.

Another important result derived from the present study was that most GCA patients who suffered a vertebrobasilar stroke had the neurologic complication after the onset of corticosteroid therapy. This observation suggests that other factors besides the GCA might play a role in the pathogenesis of the complication. In this respect, Conn et al[9] suggested that in vasculitis, corticosteroids may promote vascular occlusion because platelet thromboxane, relatively unaffected by these agents, could facilitate platelet aggregation. This fact might speak in favor of the routine use of antiaggregation at the onset of corticosteroid therapy. However, previous studies have disclosed conflicting results regarding the correlation of platelet inhibition and ischemic events in GCA. A retrospective study found low-dose aspirin effective in reducing the frequency of cranial ischemic complications of GCA.[36] In contrast, in northwestern Spain, no statistically significant reduction in the incidence of severe ischemic manifestations of GCA was observed in patients on antiaggregation before the onset of GCA symptoms compared with the remaining biopsy-proven GCA patients.[26,34] This was also the case for a series of Swiss individuals with GCA.[4] However, it is more logical to think that the development of strokes is probably a direct effect of the vasculitis rather than a complication of the corticosteroid therapy. In this regard, considering strokes as an effect of corticosteroids would not explain why strokes occurred mainly in the posterior circulation.

In conclusion, although limitations related to the retrospective nature of this study may exist, the results derived from the analysis of the large series of uniformly diagnosed and treated patients reported in the present study support the evidence of an increased risk of strokes, in particular of vertebrobasilar stroke, at the time of diagnosis of GCA. Traditional cardiovascular risk factors and the presence of other severe ischemic complications of GCA may predict an increased risk of strokes in these patients. In contrast, the presence of a chronic inflammatory response, manifested by hemoglobin values less than 12 g/dL, may indicate some kind of protection against the development of strokes at the time of diagnosis of GCA.

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REFERENCES

1. Aiello PD, Trautmann JC, McPhee TJ, Kunselman AR, Hunder GG. Visual prognosis in giant cell arteritis. *Ophthalmology.* 1993;100:550–555.
2. Alzamora MT, Sorribes M, Heras A, Vila N, Vicheto M, Fores R, Sanchez-Ojanguren J, Sancho A; "ISISCOG Study Group," Pera G. Ischemic stroke incidence in Santa Coloma de Gramenet (ISISCOG), Spain. A community-based study. *BMC Neurol*. 2008;8:5.
3. Bengtsson B-A. Haematological observations in giant cell arteritis. *Acta Med Scand*. 1982;(Suppl)658:38–43.
4. Berger CT, Wolbers M, Meyer P, Daikeler T, Hess C. High incidence of severe ischaemic complications in patients with giant cell arteritis irrespective of platelet count and size, and platelet inhibition. *Rheumatology (Oxford)*. 2009;48:258–261.
5. Caselli RJ, Daube JR, Hunder GG, Whisnant JP. Neurologic disease in biopsy-proven giant cell (temporal) arteritis. *Neurology.* 1988;38:352–359.
6. Caselli RJ, Hunder GG. Neurologic aspects of giant cell (temporal) arteritis. *Rheum Dis Clin North Am*. 1993;19:941–953.
7. Cid MC, Font C, Oristrell J, de la Sierra A, Coll-Vinent B, Lopez-Soto A, Vilaseca J, Urbano-Marquez A, Grau JM. Association between strong inflammatory response and low risk of developing visual loss and other cranial ischemic complications in giant cell (temporal) arteritis. *Arthritis Rheum*. 1998;41:26–32.
8. Cid MC, Hernandez-Rodriguez J, Esteban MJ, Cebrian M, Gho YS, Font C, Urbano-Marquez A, Grau JM, Kleinman HK. Tissue and serum angiogenic activity is associated with low prevalence of ischemic complications in patients with giant-cell arteritis. *Circulation*. 2002;106:1664–1671.
9. Conn DL, Tompkins RB, Nichols WL. Glucocorticoids in the management of vasculitis—a double edged sword? *J Rheumatol*. 1988;15:1181–1183.
10. Gonzalez-Gay MA. Giant cell arteritis and polymyalgia rheumatica: two different but often overlapping conditions. *Semin Arthritis Rheum*. 2004;33:289–293.
11. Gonzalez-Gay MA, Alonso MD, Aguero JJ, Bal M, Fernandez-Camblor B, Sanchez-Andrade A. Temporal arteritis in a northwestern area of Spain: study of 57 biopsy proven patients. *J Rheumatol*. 1992;19:277–280.
12. Gonzalez-Gay MA, Amoli MM, Garcia-Porrua C, Ollier WE. Genetic markers of disease susceptibility and severity in giant cell arteritis and polymyalgia rheumatica. *Semin Arthritis Rheum*. 2003;33:38–48.
13. Gonzalez-Gay MA, Barros S, Lopez-Diaz MJ, Garcia-Porrua C, Sanchez-Andrade A, Llorca J. Giant cell arteritis: disease patterns of clinical presentation in a series of 240 patients. *Medicine (Baltimore)*. 2005;84:269–276.
14. Gonzalez-Gay MA, Blanco R, Abraira V, Garcia-Porrua C, Ibanez D, Garcia-Pais MJ, Rigueiro MT, Sanchez-Andrade A, Guerrero J, Casariego E. Giant cell arteritis in Lugo, Spain, is associated with low longterm mortality. *J Rheumatol*. 1997;24:2171–2176. Erratum in: J Rheumatol. 1998;25:193.

15. Gonzalez-Gay MA, Blanco R, Rodriguez-Valverde V, Martinez-Taboada VM, Delgado-Rodriguez M, Figueroa M, Uriarte E. Permanent visual loss and cerebrovascular accidents in giant cell arteritis: predictors and response to treatment. *Arthritis Rheum*. 1998;41:1497–1504.
16. Gonzalez-Gay MA, Boiardi L, Garcia-Porrua C, Macchioni P, Amor-Dorado JC, Salvarani C. Geographical and genetic factors do not account for significant differences in the clinical spectrum of giant cell arteritis in southern Europe. *J Rheumatol*. 2004;31:520–523.
17. Gonzalez-Gay MA, Garcia-Porrua C. Systemic vasculitis in adults in northwestern Spain, 1988–1997. Clinical and epidemiological aspects. *Medicine (Baltimore)*. 1999;78:292–308.
18. Gonzalez-Gay MA, Garcia-Porrua C. Epidemiology of the vasculitides. *Rheum Dis Clin North Am*. 2001;27:729–749.
19. Gonzalez-Gay MA, Garcia-Porrua C, Llorca J, Gonzalez-Louzao C, Rodriguez-Ledo P. Biopsy-negative giant cell arteritis: clinical spectrum and predictive factors for positive temporal artery biopsy. *Semin Arthritis Rheum*. 2001;30:249–256.
20. Gonzalez-Gay MA, Garcia-Porrua C, Llorca J, Hajeer AH, Branas F, Dababneh A, Gonzalez-Louzao C, Rodriguez-Gil E, Rodriguez-Ledo P, Ollier WE. Visual manifestations of giant cell arteritis. Trends and clinical spectrum in 161 patients. *Medicine (Baltimore)*. 2000;79:283–292.
21. Gonzalez-Gay MA, Garcia-Porrua C, Pineiro A, Pego-Reigosa R, Llorca J, Hunder GG. Aortic aneurysm and dissection in patients with biopsy-proven giant cell arteritis from northwestern Spain: a population-based study. *Medicine (Baltimore)*. 2004;83:335–341.
22. Gonzalez-Gay MA, Garcia-Porrua C, Vazquez-Caruncho M. Polymyalgia rheumatica in biopsy proven giant cell arteritis does not constitute a different subset but differs from isolated polymyalgia rheumatica. *J Rheumatol*. 1998;25:1750–1755.
23. Gonzalez-Gay MA, Garcia-Porrua C, Vazquez-Caruncho M, Dababneh A, Hajeer A, Ollier WE. The spectrum of polymyalgia rheumatica in northwestern Spain: incidence and analysis of variables associated with relapse in a ten-year study. *J Rheumatol*. 1999;26:1326–1332.
24. Gonzalez-Gay MA, Lopez-Diaz MJ, Barros S, Garcia-Porrua C, Sanchez-Andrade A, Paz-Carreira J, Martin J, Llorca J. Giant cell arteritis: laboratory tests at the time of diagnosis in a series of 240 patients. *Medicine (Baltimore)*. 2005;84:277–290.
25. Gonzalez-Gay MA, Miranda-Filloy JA, Lopez-Diaz MJ, Perez-Alvarez R, Gonzalez-Juanatey C, Sanchez-Andrade A, Martin J, Llorca J. Giant cell arteritis in northwestern Spain: a 25-year epidemiologic study. *Medicine (Baltimore)*. 2007;86:61–68.
26. Gonzalez-Gay MA, Pineiro A, Gomez-Gigirey A, Garcia-Porrua C, Pego-Reigosa R, Dierssen-Sotos T, Llorca J. Influence of traditional risk factors of atherosclerosis in the development of severe ischemic complications in giant cell arteritis. *Medicine (Baltimore)*. 2004;83:342–347.
27. Gonzalez-Gay MA, Vazquez-Rodriguez T, Lopez-Diaz MJ, Miranda-Filloy JA, Gonzalez-Juanatey C, Martin J, Llorca J. The epidemiology of giant cell arteritis and polymyalgia rheumatica. Arthritis Rheum. 2009 (in press).
28. Gonzalez-Juanatey C, Lopez-Diaz MJ, Martin J, Llorca J, Gonzalez-Gay MA. Atherosclerosis in patients with biopsy-proven giant cell arteritis. *Arthritis Rheum*. 2007;57:1481–1486.
29. Graham E, Holland A, Avery A, Russell RW. Prognosis in giant-cell arteritis. *Br Med J*. 1981;282:269–271.
30. Gran JT, Myklebust G, Wilsgaard T, Jacobsen BK. Survival in polymyalgia rheumatica and temporal arteritis: a study of 398 cases and matched population controls. *Rheumatology (Oxford)*. 2001;40:1238–1242.
31. Hellmann DB. Temporal arteritis: a cough, toothache, and tongue infarction. *JAMA*. 2002;287:2996–3000.
32. Hunder GG, Bloch DA, Michel BA, Stevens MB, Arend WP, Calabrese LH, Edworthy SM, Fauci AS, Leavitt RY, Lie JT, Lightfoot RW, Masi AT, McShane DJ, Mills JA, Wallace SL, Zvaifler NJ. The American College of Rheumatology 1990 criteria for the classification of giant cell arteritis. *Arthritis Rheum*. 1990;33:1122–1128.
33. Levine SM, Hellmann DB. Giant cell arteritis. *Curr Opin Rheumatol*. 2002;14:3–10.
34. Lopez-Diaz MJ, Llorca J, Gonzalez-Juanatey C, Pena-Sagredo JL, Martin J, Gonzalez-Gay MA. The erythrocyte sedimentation rate is associated with the development of visual complications in biopsy-proven giant cell arteritis. *Semin Arthritis Rheum*. 2008;38:116–123.
35. Matteson EL, Gold KN, Bloch DA, Hunder GG. Long-term survival of patients with giant cell arteritis in the American College of Rheumatology giant cell arteritis classification criteria cohort. *Am J Med*. 1996;100:193–196.
36. Nesher G, Berkun Y, Mates M, Baras M, Rubinow A, Sonnenblick M. Low-dose aspirin and prevention of cranial ischemic complications in giant cell arteritis. *Arthritis Rheum*. 2004;50:1332–1337.
37. Nordborg E, Bengtsson BA. Death rates and causes of death in 284 consecutive patients with giant cell arteritis confirmed by biopsy. *BMJ*. 1989;299:549–550.
38. Nuenninghoff DM, Hunder GG, Christianson TJ, McClelland RL, Matteson EL. Incidence and predictors of large-artery complication (aortic aneurysm, aortic dissection, and/or large-artery stenosis) in patients with giant cell arteritis: a population-based study over 50 years. *Arthritis Rheum*. 2003;48:3522–3531.
39. Pego-Reigosa R, Garcia-Porrua C, Pineiro A, Dierssen T, Llorca J, Gonzalez-Gay MA. Predictors of cerebrovascular accidents in giant cell arteritis in a defined population. *Clin Exp Rheumatol*. 2004;22 (6 Suppl 36):S13–17.
40. Reich KA, Giansiracusa DF, Strongwater SL. Neurologic manifestations of giant cell arteritis. *Am J Med*. 1990;89:67–72.
41. Rueda B, Lopez-Nevot MA, Lopez-Diaz MJ, Garcia-Porrua C, Martin J, Gonzalez-Gay MA. A functional variant of vascular endothelial growth factor is associated with severe ischemic complications in giant cell arteritis. *J Rheumatol*. 2005;32:1737–1741.
42. Salvarani C, Cantini F, Boiardi L, Hunder GG. Polymyalgia rheumatica and giant-cell arteritis. *N Engl J Med*. 2002;347:261–271.
43. Salvarani C, Della Bella C, Cimino L, Macchioni P, Formisano D, Bajocchi G, Pipitone N, Catanoso MG, Restuccia G, Ghinoi A, Boiardi L. Risk factors for severe cranial ischaemic events in an Italian population-based cohort of patients with giant cell arteritis. *Rheumatology (Oxford)*. 2009;48:250–253.
44. Turney TM, Garraway WM, Whisnant JP. The natural history of hemispheric and brainstem infarction in Rochester, Minnesota. *Stroke*. 1984;15:790–794.