Predictors of cerebrovascular accidents in giant cell arteritis in a defined population

R. Pego-Reigosa[1], C. Garcia-Porrua[2], A. Piñeiro[2], T. Dierssen[3], J. Llorca[3], M.A. Gonzalez-Gay[2]

Divisions of Neurology[1] and Rheumatology[2], Hospital Xeral-Calde, Lugo; Division of Preventive Medicine and Public Health[3], School of Medicine, University of Cantabria, Santander, Spain.

Dr Llorca and Dr Gonzalez-Gay share senior authorship in this study.

Robustiano Pego-Reigosa, MD, PhD; Miguel A. Gonzalez-Gay, MD, PhD; Carlos Garcia-Porrua MD, PhD; Angela Piñeiro, MD; Trinidad Dierssen, MD, PhD; Javier Llorca, MD, PhD.

Please address correspondence to: Dr. Miguel A. González-Gay, Division of Rheumatology, Hospital Xeral-Calde, c/ Dr. Ochoa s/n, 27004 Lugo, Spain. E-mail: miguelaggay@hotmail.com

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ABSTRACT

Objective. *To examine the frequency and predictors of cerebrovascular accidents (CVA) in giant cell arteritis (GCA) patients from a defined population.*

Methods. *Retrospective study of biopsy-proven GCA patients diagnosed from 1981 through 2001 at the single hospital for the population of Lugo (Northwest Spain).*

Results. *Thirty (14.3%) of the 210 biopsy-proven GCA patients had CVA, 5 of them (16.7%) involving the vertebrobasilar territory. Five patients (4 of them involving the carotid territory) had CVAwithin the 2 years prior to the onset of GCA symptoms. Four patients had CVA within the first month after the diagnosis of the disease. Of these, 3 involved the vertebrobasilar territory. Another 5 patients suffered carotid stroke between the 4th and the 12th month after the disease diagnosis. The remaining 16 GCA patients had CVA (all but one involving the carotid territory) at least 1 year after the diagnosis of vasculitis. No differences in the clinical and laboratory features at the time of diagnosis between patients who had CVA and the rest of the biopsy-proven GCA patients were observed. However, hypertension and hyperlipidemia at the time of diagnosis of GCA were associated with the development of CVA ($p<0.05$ for both). Also, anemia at the time of diagnosis (hemoglobin < 12 g/dL) [hazard ratio = 0.34 {95% CI 0.12 - 1.00; p = 0.05}] was negatively associated with CVA within the first 10 years after the diagnosis of the disease. Mortality in GCA patients with CVA was not significantly higher than that in patients without CVA (hazard ratio=1.53; p= 0.14).*

Conclusion. *The present study confirms that CVA may occur in GCA. Vertebrobasilar accidents are more common than carotid accidents at the time of diagnosis of the disease. Vascular risk factors should be carefully controlled in the follow-up of GCA patients.*

Introduction

Giant cell arteritis (GCA) is the most common vasculitis in elderly people in Western countries (1). It usually involves the large and medium-sized blood vessels with a predisposition to the cranial arteries (2, 3).

Cerebrovascular accidents (CVA) have been extensively reported in GCA patients (4-8). In this regard, vertebrobasilar strokes are more common than in the general population (5,9). However, although CVA, particularly due to involvement of the vertebrobasilar territory, were reported to be a significant cause of early mortality and morbidity (6,10), they did not appear to be a late complication of GCA(10).

An important step forward might be to assess the frequency of CVA during the follow-up in unselected GCA patients, whether those with CVA have distinctive clinical features at the time of diagnosis, and whether there are some factors that might predict the development of CVA. To address these questions we have examined the frequency of CVA in a series of biopsy-proven GCAcases diagnosed at the single hospital for a defined population.

Patients and methods

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 1981 and December 2001 was undertaken. This is the only referral center for a well-defined population of nearly 250,000 people living in the middle of the province of Lugo, in Northwest Spain (8).

Patients were diagnosed with biopsy-proven GCA as reported elsewhere (8, 11). They were uniformly treated for their condition. After a diagnosis was established, therapy with oral corticosteroids was started (generally 40 to 60 mg of prednisone in 3 doses per day for 3-4 weeks). Patients with visual manifestations were often treated with daily intravenous pulse methylprednisolone (1g/day for 3 consecutive days) followed by 60 mg/prednisone/day for 3-4 weeks. The prednisone dose was then gradually tapered, as follows: by 10 mg every 2 weeks to arrive at 40 mg/day; and a further reduction by 5 mg every 2 weeks to arrive at 20 mg/day. The prednisone reduction below 20 mg/day was slower and individualized; a rate of 2.5 mg every 2-3 months was generally attempted. When a relapse of the disease was suspected (flare of GCA features, which were suppressed by a resumption of or increase in the corticosteroid dose), prednisone was generally increased to 10 mg above the previous effective dose.

Each patient was assessed for any evidence of CVA within 2 years prior to, at the diagnosis of GCA, or thereafter. A patient was considered to have CVA related to GCA when he/she had stroke and/or transient ischemic attacks (TIA). Strokes were classified according to their clinical features and were confirmed by computed tomography or magnetic resonance imaging. TIA were diagnosed if the symptoms were self-limiting within less than 24 hours, without residual neurological damage (7, 8).

Data collection

Besides demographic features, a history of hypertension, hyperlipidemia, smoking, and diabetes mellitus at the time of diagnosis of GCA and data on the following items were analyzed: delay to the diagnosis of the disease from the onset of symptoms, headache, constitutional syndrome (asthenia, anorexia and weight loss of at least 4 kg), abnormal temporal artery on physical examination, jaw claudication, polymyalgia rheumatica, fever (temperature greater than 38ºC), visual manifestations (transient visual loss including amaurosis fugax, permanent visual loss, and diplopia), and CVA. Also, the erythrocyte sedimentation rate (ESR) and hemoglobin at the time of diagnosis were assessed in all patients. Information about follow-up was examined.

Transient visual loss was considered to be related to GCA when it occurred in association with other clinical manifestations of this vasculitis and/or a significant elevation of ESR and the temporal artery biopsy showed disruption of the internal elastic laminae with infiltration of mononuclear cells into the arterial wall with or without giant cells.

Statistical analysis

Rates were reported as cases per 100,000 population 50 years or older. They were calculated using the number of new cases observed/population 50 years of age and older. In order to compare these rates with CVA mortality in the general Spanish population, we estimated the standardized mortality ratio adjusting for age and sex (indirect method) (12). Continuous data were described as the mean and standard deviation (mean ± SD), and categorical variables as %ages. Equality of means was tested by the Student's t-test. Proportions were compared using the Chi-square or Fisher's exact tests. Predictive variables were defined as variables that had to be present prior to or at the time of diagnosis with GCA. Possible predictive variables for the development of CVA were assessed using Cox proportional hazard regression. Hazard ratios and their 95% confidence intervals (CI) were assessed. CVA cumulative hazards were estimated using the Nelson-Aalen method. For the survival analysis, a cerebrovascular event was considered to be a "failure". GCA patients who were alive without any cerebrovascular event at the last follow-up or at the end of this study or who had died for any cause other than CVA were considered to be "censored individuals". All statistical analyses were performed using the package Stata 8/SE (Stata Intercooled, College Station, TX).

Results

Temporal relationship between CVA and GCA

During the study period 210 patients were diagnosed with biopsy-proven GCA. Thirty patients (14.3%) had at least one cerebrovascular event, 5 of them (16.7%) involving the vertebrobasilar territory. Seven of the 30 GCA patients with CVA had TIA and 23 had strokes.

Five patients had CVA prior to the onset of GCA symptoms (4 of them involving the carotid territory). Among them, one patient suffered a TIA 14 months before disease diagnosis, another had a carotid stroke 2 years before, 2 had carotid strokes within the year before (11.5 and 10.5 months) and one patient had a vertebrobasilar stroke 18 months before the onset of GCA symptoms.

Four of the 30 patients had a cerebrovascular event within the first month after the diagnosis of the disease. Of these, 3 involved the vertebrobasilar territory. Another 5 patients suffered carotid stroke between the 4th and the 12th month after the diagnosis of GCA. The remaining 16 GCA patients suffered CVA (all but one involving the carotid territory) at least 1 year after the diagnosis of the vasculitis.

A 72-year-old man died because of a vertebrobasilar accident 72 hours after the onset of corticosteroid therapy (7). Apart from this patient, no other GCA patients died as a consequence of CVA within the first year after the diagnosis. However, during their follow-up 7 more patients died because of CVA or their complications.

Incidence and mortality

The linearized incidence rate of CVA in biopsy-proven GCA from Lugo was 2,781/100,000 person-years in people 50 years and older. Regrettably, at present, data on the incidence of CVA in the Lugo area or in the Spanish population 50 years and older are not available.

In a former study we observed that mortality in GCA patients was not higher than that observed in the general population of the same age in Lugo (13). In the present study we have found that mortality in biopsy-proven GCA patients who had CVA was not significantly higher than that observed in biopsy-proven GCApatients without

CVA (hazard ratio = 1.53; p = 0.14). The standardized mortality ratio in biopsy-proven GCA due to CVA was 1.17 using the Spanish population 50 years and older as a reference (12).

Differences in the clinical spectrum of GCA at the time of diagnosis between patients with and without CVA

No differences in age, gender, delay to diagnosis from the onset of GCA symptoms and clinical and laboratory features of GCA at the time of diagnosis between patients with CVA and the rest of biopsy-proven GCA patients were observed (Table I).

Also, no statistically significant differences in the rate of prednisone reduction between GCA patients with or without a history of CVA were found (data not shown).

Predictors and correlates of CVA in GCA

Based on a prolonged follow-up (mean ± SD: 62 ± 50 months; range: 3 days to 240 months) no clinical feature of GCA was found to be a predictor of CVA. However, hypertension and hyperlipidemia at the time of diagnosis of GCA were associated with the development of CVA ($p < 0.05$ for both). Also, anemia (due to chronic disease) at the time of diagnosis (hemoglobin <12 g/dL) [hazard ratio = 0.34 {95%CI 0.12- 1.00; p = 0.05}] was negatively associated with CVA within the first 10 years after the diagnosis of the disease. However, in a longer follow-up this apparent negative association was not observed [hazard ratio = 0.52 {95% CI 0.22 - 1.23; p = 0.13}]. The Cox proportional hazard model for the best predictors of CVAis shown in Table II.

Figure 1 shows the probability of having a cerebrovascular event in GCApatients with or without anemia (Nelson-Aalen cumulative hazard curve).

Table I. Comparison of clinical and laboratory features at the time of diagnosis between patients with cerebrovascular accidents (CVA) and the remainder of the biopsy-proven GCApatients.

Variable	Without CVA (n =180) (85.7%)*	With CVA (n =30) (14.3%)*	p
Age at diagnosis (years ±SD)	74.8 ± 6.9	73.3 ± 7.5	0.28
Women	95 (52.8)	18 (60.0)	0.46
Delay to diagnosis (weeks)**	10.3 ± 11.4	11.1 ±12.2	0.70
Headache	157 (87.2)	26 (86.7)	0.93
Constitutional syndrome#	115 (63.9)	20 (66.7)	0.77
Abnormal temporal arteries##	137 (76.1)	22 (73.3)	0.74
Jaw claudication	75 (41.7)	11 (36.7)	0.61
Polymyalgia rheumatica	78 (43.3)	9 (30.0)	0.17
Fever (temperature ≥ 38ºC)	17 (9.4)	4 (13.3)	0.51
Visual manifestations	40 (22.2)	9 (30.9)	0.35
Permanent visual loss	21 (11.7)	6 (20.0)	0.21
ESR (mean ±SD) mm/1st h.	93.2 ±22.3	92.1 ± 23.2	0.81
Hemoglobin (mean ±SD) g/dL	11.7 ± 1.6	11.8 ± 1.6	0.80

*Number in parenthesis indicates the total proportion of patients with a particular variable.
**From the onset of symptoms until the time in which the diagnosis of the disease was made.
#Constitutional syndrome: asthenia, anorexia and weight loss of at least 4 kg.
##Abnormal temporal arteries on physical examination.

Table II. Best predictors of CVAin biopsy-proven GCApatients from Northwest Spain.

Variable*	Hazard ratio	95% Confidence interval	p
Hypertension	2.68	1.29 – 5.59	0.009
Hyperlipidemia	2.37	1.04 – 5.38	0.039
Anemia	0.52	0.22 – 1.23	0.138
Anemia**	0.34	0.12 – 1.00	0.050

*At the time of diagnosis of GCA.
** From the time of diagnosis until 120 months of follow-up.

Discussion

Although most cases of GCA involve the temporal artery, involvement of the larger arteries has also been described in about 10% of patients (14). The internal carotid system, distinct from its ophthalmic branches, the vertebrobasilar arterial system and the circle of Willis have been reported to be involved in GCA (15). As was long ago pointed out by Wilkinson and Russell (16), once the vessels perforate the dura they are not usually involved in GCA, since at this location they lose elastic fibers in the media, and the external elastic lamina disappears.

Caselli *et al.* reported CVA (TIA or strokes) in 12 (7.2%) of 166 biopsy-proven GCA patients (15). Four of them had CVA in the vertebrobasilar territory and the remaining 8 involved the carotid system (15). However, CVA in elderly people are generally due to conditions unrelated to GCA such as hypertension or atherosclerotic disease. Thus, the exact frequency of CVA that are directly related to GCA is difficult to be established.

In our series 4 (1.9%) of the 210 biopsy-proven GCA patients developed CVA shortly after the diagnosis of the disease and, due to this, we may assume that in these patients the inflammation of the vessels related to the arteritic disease played an important role in the development of CVA. In these cases CVA would be probably disease related. Another 5 patients developed CVA within the first year after the disease diagnosis. In these patients, it is possible that the presence of a smolder disease might also play a role in the development of CVA. However, as all of these 5 patients were in treatment with steroids at the time of the cerebrovascular event, the possibility that prednisone, not GCA, was the real risk factor for CVA should be considered.

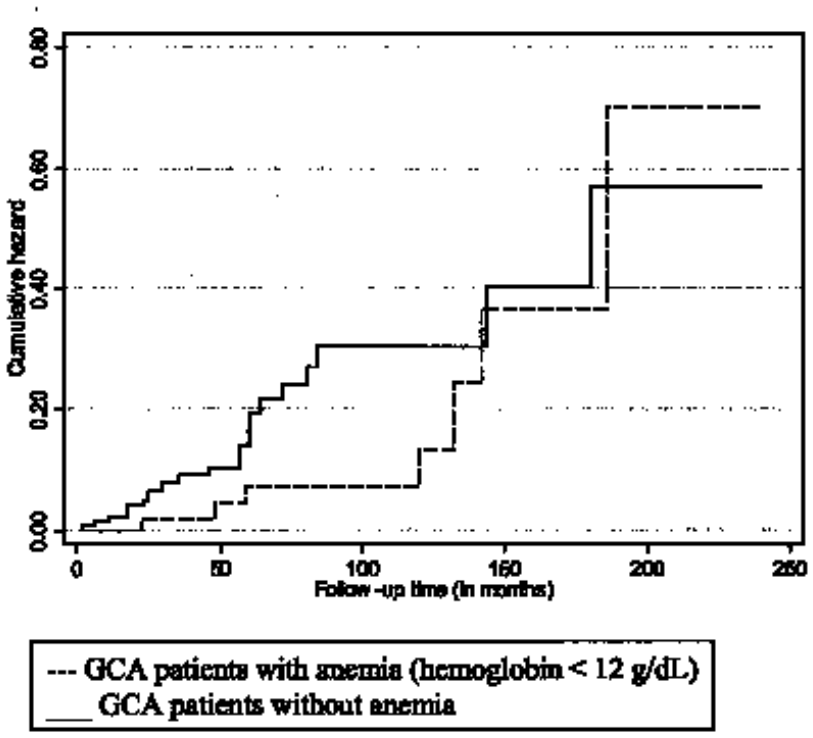

Fig. 1. Probability of having a cerebrovascular event in patients with biopsy-proven GCA. **Continuous line**: GCA patients without anemia; **dashed line**: GCA patients with anemia (hemoglobin < 12 g/dL).

Likewise, we cannot completely exclude that a silent (subclinical) GCA might have been implicated in the pathogenesis of some of the CVA that occurred within the 2 years before the diagnosis of the disease. However, none of these patients had clinical features of GCAat the time of the CVA. Late CVA events observed in this series of GCA patients may probably be related to classic vascular risk factors.

In population-based epidemiologic studies of cerebral infarction the ratio of patients with carotid accidents to those with vertebrobasilar events was 5:1 (9). This was also the ratio observed in our series when all patients with CVA were considered regardless of the temporal relationship between the diagnosis of GCA and the development of CVA. However, in keeping with previous reports (4, 15), this ratio changed dramatically when CVA occurred within the first month after the diagnosis of the disease.

At present, the possible relationship between the development of CVA and other clinical features of GCAis poorly understood. Our results only suggest a possible protective role of anemia, as a marker of a chronic and severe inflammatory response, for the development of CVA. However, none of the classic clinical features of the disease was found to be a predictor for CVA. Former studies have suggested a protective effect of anemia for the development of severe ischemic complications, in particular irreversible blindness (8, 17). Cid *et al*. have confirmed that a strong inflammatory response has an angiogenic activity, which may have a compensatory effect for ischemia in GCA patients (18). This fact might, at least in part, explain the potential protective role of anemia for the development of CVA within the first 10 years after the disease diagnosis.

Hypertension and hyperlipidemia are well known factors that predispose to CVA (19). These factors were also predictors of CVA in our series of GCA patients. The high ratio of CVA in the carotid to the vertebrobasilar territory in patients with CVA occurring after one year of follow-up (15:1) may suggest that these factors are more important once the disease has been treated.

In conclusion, although the major limitation of the present study is its retrospective nature, our observations confirm that CVA may occur in GCA patients. Vertebrobasilar accidents are more common than carotid accidents at the time of diagnosis of the disease. Increased awareness of these complications in GCA, particularly in patients with hypertension and hyperlipidemia, is needed. Vascular risk factors should be carefully controlled in the follow-up of GCA patients. Further investigations, including a prospective study using a control group (with the same age, gender, common risk factors of CVA, and similar genetic background to the GCApatients), are required to fully determine the causes of CVAin GCA.

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