Ischemic Heart Disease in Patients from Northwest Spain with Biopsy Proven Giant Cell Arteritis. A Population Based Study

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ABSTRACT. ***Objective.*** To assess the incidence, mortality, and predictors of ischemic heart disease (IHD) in patients from the Lugo region of Northwest Spain with biopsy-proven giant cell arteritis (GCA).

Methods. Retrospective study of patients with biopsy-proven GCA diagnosed from 1981 to 2001 at the single hospital for a population of 250,000 people. A survival analysis was performed. Hazard ratios and standardized mortality ratio (SMR) as well as predictors of IHD in patients with biopsy-proven GCA were also assessed.

Results. Nineteen (9%) of the 210 patients with biopsy-proven GCA diagnosed during the period of study had IHD. The incidence of IHD in patients with GCA was 12.6/1000 person-years at risk (95% CI 6.9–21.0). During the study period 1981–2000 the population aged ≥ 50 years in Lugo was roughly 100,000, and the mortality rate due to IHD in patients with GCA for that population was 8/100,000. The SMR in patients with GCA due to IHD was 1.62 (95% CI 0.70–3.20). Mortality in patients with GCA who had IHD was higher than in those patients without IHD (age and sex adjusted hazard ratio 2.81, 95% CI 1.51–5.21; p = 0.001). Age (hazard ratio 1.15), hypertension (hazard ratio 2.51), and abnormal temporal artery on physical examination (hazard ratio 0.36) at the time of diagnosis of GCA were the best predictors of IHD over the followup period in patients with biopsy-proven GCA.

Conclusion. Our observations suggest that mortality due to IHD in patients from Lugo with GCA is not much higher than that reported in the Spanish population aged 50 years and older. However, mortality in patients with GCA with IHD is higher than in GCA patients without IHD. (J Rheumatol 2005;32:502–6)

Key Indexing Terms:
GIANT CELL ARTERITIS
ISCHEMIC HEART DISEASE
MORTALITY
TEMPORAL ARTERY BIOPSY
PREDICTORS

Giant cell arteritis (GCA) is one of the most common forms of vasculitis in North America and Europe[1]. It is characterized by granulomatous involvement of large and medium-size blood vessels of the aorta with predilection for the extracranial arteries of the carotid artery[2,3]. Its frequency increases with aging and peaks in patients older than 70 years[4]. In addition to well reported visual complications[5-7], inflammatory involvement of arteries may yield cerebrovascular complications[6-8] or aortic aneurysm disease[9,10].

Pathological studies have confirmed that coronary vasculitis may also occur in patients with GCA[11]. Uddhammar, *et al* reported an increased mortality due to cardiovascular complications, including ischemic heart disease (IHD), in patients with GCA from Northern Sweden[12]. However, extensive information on IHD in patients with GCA is not available. The literature on IHD in GCA is scarce and generally limited to case reports[13-16].

To further investigate this issue, we determined the incidence of this complication in patients with biopsy-proven GCA from a well defined population of Lugo in Northwest Spain[5,17]. Also, we attempted to identify clinical features of GCA that could be associated with an increased risk of IHD in these patients.

MATERIALS AND METHODS

Study population. A retrospective review of case records of all patients diagnosed with biopsy-proven GCA at the Department of Medicine of the

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Hospital Xeral-Calde between January 1981 and December 2001 was performed. This hospital is the reference center for a mixed rural and urban population of almost a quarter of a million people. Information about the characteristics of this Caucasian population has been described[5,17].

Diagnosis of GCA. Temporal artery biopsy (TAB) procedure in Lugo patients has been reported[18,19]. Patients were diagnosed with GCA when TAB showed a compatible pathology report, describing the characteristic mononuclear cell infiltration of the arterial wall, with or without granulomas and/or multinucleated giant cells.

Clinical definitions. Clinical definitions of GCA manifestations and treatment in the Lugo population have been reported[5,17,19].

Information about smoking history, blood pressure, and cholesterol and glucose levels was available in all cases at the time of disease diagnosis. Smoking history was treated as a dichotomous variable (heavy vs non-heavy smoking) in this analysis. Heavy smokers comprised those patients who still smoked at disease diagnosis or who had smoked within 10 years before onset of GCA symptoms. The remaining patients (non-heavy smokers) included those who never smoked or had stopped smoking at least 10 years before disease onset[10].

Clinical presentation of IHD included acute coronary syndromes with or without persistent ST-segment elevation and chronic coronary heart disease. IHD was diagnosed if any of the following criteria were satisfied: a recorded diagnosis of ischemic cardiopathy, prior admission on account of some acute coronary syndrome (acute myocardial infarct or unstable angina), the presence of pathological Q waves in the electrocardiogram obtained during hospitalization, and coronary images showing > 50% stenosis of at least one coronary vessel. Ischemic dilated cardiomyopathy was also included in this category if the patient had shown deteriorated systolic function and a dilated left ventricle with evidence of ischemic cardiopathy by echocardiographic and/or catheterization studies.

Data collection. Demographic and clinical data at the time of diagnosis of all the patients with GCA were analyzed. Also, erythrocyte sedimentation rate (ESR), hemoglobin, platelet count, cholesterol, and glucose on admission at the time of diagnosis of GCA were assessed. In assessing followup, medical records of all patients with biopsy-proven disease were reviewed by Lugo physicians (MAG-G, AP, CG-P, and RP-R). For the purpose of this study, only information found in the medical records was considered. Thus, telephone interview or information about the patients given by their relatives was not considered.

Statistical analysis. Categorical variables were compared with the chi-squared test or Fisher exact test; equality of means in continuous variables was tested with the Student t test. A survival analysis was performed to determine factors associated with IHD. To do so, patients with IHD previous to the GCA diagnosis were excluded. IHD after GCA diagnosis was considered as failure, and deaths by other causes or end of the followup without IHD were considered censored. Hazard ratios and 95% confidence intervals (CI) were estimated by multivariate Cox regression, including all variables with p values lower than 0.20. Standardized mortality ratio (SMR) and 95% CI were calculated for the whole series of patients with biopsy-proven GCA who had IHD. Also, they were calculated separately for men and women with biopsy-proven GCA who had IHD.

Statistical significance was defined as $p \leq 0.05$. All statistical analyses were performed using the software SPSS v. 11.5 and Stata 8/SE.

RESULTS

IHD in patients with GCA: incidence and mortality. Nineteen (9%) of the 210 patients with GCA diagnosed in Lugo between 1981 and 2001 had IHD. Three had IHD before the onset of GCA symptoms. Another had IHD one year before the onset of GCA but also had angina at the time of diagnosis of GCA, and 15 months and 9 years after GCA diagnosis. One woman, sent to hospital because of GCA associated with tongue necrosis, had thrombosis of both external carotids and died because of acute myocardial infarction during admission. Two patients receiving prednisone treatment had IHD within the first year after diagnosis. Another 2 patients with no history of coronary syndromes experienced IHD between the first and second year after disease diagnosis while they were receiving low doses of prednisone (< 10 mg/day in both cases). The remaining 10 patients had IHD between the second and the twelfth year after diagnosis of GCA (median 5 yrs).

The incidence of IHD in GCA was 12.6/1000 person-years at risk (95% CI 6.9–21.0). There were 100,000 individuals in Lugo aged 50 years and older during the period 1981–2001, and the mortality due to IHD in GCA was 8/100,000. SMR in patients with GCA due to IHD using the Spanish population 50 years and older as a reference was 1.62 (95% CI 0.70–3.20). SMR related to IHD was not different when patients with GCA were assessed by sex, since in both subgroups the 95% CI included 1.0 [men 1.21 (95% CI 0.33–3.09); women 2.47 (95% CI 0.67–6.32)]. However, the significance of these results is limited because of the small number of deaths (4 men, 4 women).

Mortality in patients with GCA who had IHD was higher than that observed in patients without IHD [crude hazard ratio 3.42 (95% CI 1.85–6.33), $p < 0.001$; age and sex adjusted hazard ratio 2.81 (95% CI 1.51–5.21), $p = 0.001$]. Figure 1 shows that probability of survival was reduced in the group of patients who developed IHD. Figure 2 shows the proportion of survivors not experiencing IHD events over time.

Differences between patients with GCA with or without IHD. Epidemiological and clinical differences at the time of GCA diagnosis between patients with or without IHD are shown in Table 1 and 2.

When a diagnosis of GCA was made, patients who had IHD were older than the remaining GCA patients (78.1 ± 6.7 vs 74.3 ± 6.9 yrs in those without IHD; $p = 0.023$). No differences according to sex, delay to the diagnosis, site of residence, or duration of followup between patients with or without IHD were found (Table 1). However, when traditional risk factors for atherosclerosis were examined some differences were observed (Table 1). With respect to this, 11 (58%) of the 19 patients with IHD had hypertension at the time of GCA diagnosis compared to 59 (31%) of 191 without this complication ($p = 0.017$). GCA patients with IHD more commonly had a history of hypercholesterolemia or diabetes mellitus, but the differences did not achieve statistical significance (Table 1).

Patients with GCA with or without IHD did not exhibit statistically significant differences in the clinical features of the disease (Table 2). This was also the case when differences in the laboratory markers of inflammatory response were assessed (Table 2).

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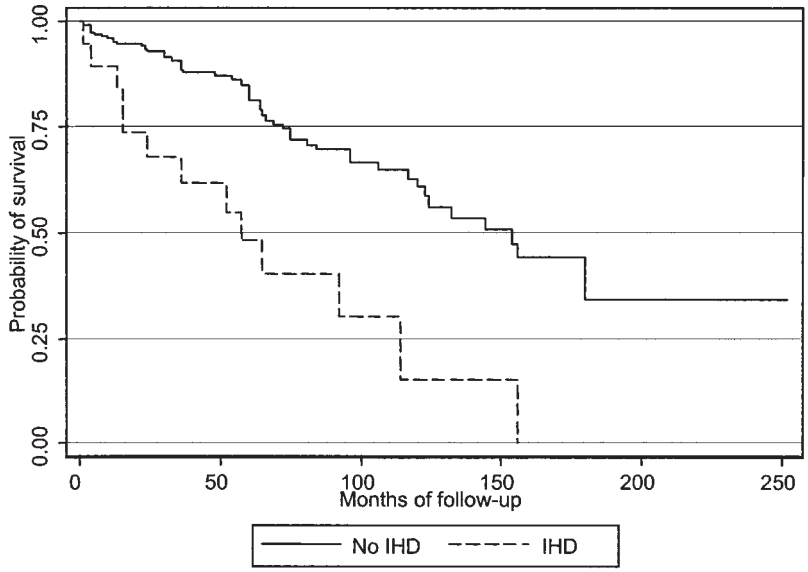

Figure 1. Probability of survival in patients with GCA with or without IHD.

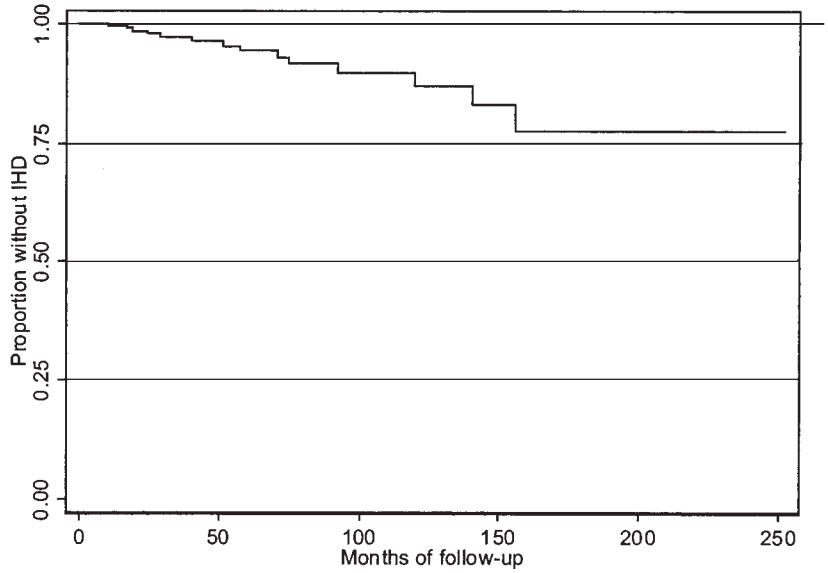

Figure 2. Proportion of survivors not experiencing IHD events over time.

Table 1. Epidemiological differences at the time of diagnosis between patients with biopsy-proven GCA with or without ischemic heart disease (IHD).

Variable	With IHD, n = 19 (%)	Without IHD, n = 191 (%)	p
Age, yrs (mean ± SD)	78.1 ± 6.7	74.3 ± 6.9	0.023
Men/women	9 (47.4)/10 (52.6)	88 (46.1)/103 (53.9)	0.91
Time to diagnosis, wks (mean ± SD)*	12.2 ± 10.1	10.2 ± 11.6	0.47
Followup, mo (mean ± SD)	52.5 ± 42.5 Median 45, IQR 15–84	66.8 ± 52.5 Median 54, IQR 25–90	0.25
Rural/urban	12 (63.2)/7 (36.8)	120 (62.8)/71 (37.2)	0.98
Hypercholesterolemia	4 (21.1)	24 (12.6)	0.30
Heavy smokers	2 (10.5)	29 (15.2)	0.59
Hypertension	11 (57.9)	59 (30.9)	0.017
Diabetes mellitus	3 (15.8)	14 (7.3)	0.20

* From the onset of symptoms until the time the diagnosis of GCA was made.

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Table 2. Clinical differences at the time of diagnosis between patients with biopsy-proven GCA with or without ischemic heart disease (IHD).

Variable	With IHD, n = 19 (%)	Without IHD, n = 191 (%)	p
Headache	17 (89.5)	166 (86.9)	0.87
Abnormal temporal artery*	12 (63.2)	147 (77.0)	0.18
Scalp tenderness	5 (26.3)	67 (35.1)	0.44
Constitutional syndrome**	14 (73.7)	121 (63.4)	0.37
Fever ≥ 38° C	1 (5.3)	20 (10.5)	0.70
Jaw claudication	8 (42.1)	78 (41.0)	0.92
Dysphagia	3 (15.8)	8 (4.2)	0.07
PMR	10 (52.6)	77 (40.3)	0.30
Visual manifestations	4 (21.1)	45 (23.6)	0.81
Permanent visual loss	2 (10.5)	25 (13.1)	1.00
Cerebrovascular accidents	0 (0.0)	4 (2.1)	1.00
Limb claudication of recent onset	0 (0.0)	6 (3.1)	1.00
ESR, mm/h (mean ± SD)	88 ± 42	93 ± 22	0.35
Hemoglobin, g/dl (mean ± SD)	11.6 ± 1.5	11.8 ± 1.6	0.61
Hemoglobin < 12 g/dl	9 (47.4)	59 (30.9)	0.14
Platelets (× 1000)/mm^3 (mean ± SD)	398 ± 135	411 ± 136	0.70

* On physical examination. ** Asthenia, anorexia, and weight loss of at least 4 kg. PMR: polymyalgia rheumatica.

Predictors of IHD in patients with GCA. Age (hazard ratio 1.15) and hypertension (hazard ratio 2.51) were the best positive predictors of IHD at time of diagnosis of GCA (Table 3). In contrast, the presence of abnormal temporal artery on physical examination at the time of GCA diagnosis (hazard ratio 0.36) was found to be a negative predictor of IHD over the followup in patients with GCA (Table 3).

DISCUSSION

This is the first population based study on the incidence of IHD in Southern European patients diagnosed with GCA.

Increased mortality due to vascular complications as a consequence of lack of control of inflammation, including myocardial infarction, early after GCA diagnosis has been described[20]. In this regard, neither of the 2 patients with GCA reported by Save-Soderbergh, *et al* who died of myocardial infarction was receiving adequate steroid treatment when symptoms of IHD occurred[21]. IHD has been also observed shortly after disease diagnosis despite high-dose steroid therapy[13]. However, in this study we found a low frequency of IHD within the first month after onset of steroid treatment.

It is possible that adequate therapy might be useful in preventing this complication since reports have described a low incidence of IHD in followup studies of GCA[4,22]. However, although prednisone therapy might diminish the potential role of GCA in enhancing the development of IHD, this therapy may yield a possible potentiation of traditional atherosclerosis risk factors. Also, subclinical vascular inflammation may continue for several years after onset of steroid treatment. With respect to this, as described in a study in Rochester, Minnesota, USA, where GCA incidence is high[9], we also observed the development of aneurysmal disease in the followup of our patients with GCA, in particular in those with hypertension and severe inflammatory response at diagnosis of vasculitis[10].

Due to atherosclerosis and subclinical inflammation, IHD might be a potential complication several years after GCA diagnosis. In this regard, investigators from the reference center for patients with polymyalgia rheumatica and GCA from 5 northern counties in Sweden described an increased mortality due to IHD in a followup of GCA[12]. In contrast, in a previous study we observed that the overall mortality in GCA patients was not higher than that observed in the general population of the same age in Lugo[23]. In this study we observed that the SMR in patients with biopsy-

Table 3. Hazard ratios for ischemic heart disease in patients with biopsy-proven GCA by multiple Cox regression.

Variable	Hazard Ratio	95% CI		p
		Lower	Higher	
Age (each year)	1.15	1.04	1.26	0.004
Hypertension	2.51	0.87	7.25	0.089
Abnormal temporal artery on physical examination	0.36	0.11	1.13	0.080

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proven GCA from Lugo due to IHD was not much higher than that reported for the Spanish population aged 50 years and older. Different genetic backgrounds and potential referral bias of the populations may account for these different results.

We found that GCA patients with IHD were older and had more traditional risk factors for atherosclerosis, in particular hypertension, than those who did not have IHD. These features and a normal temporal artery on physical examination at diagnosis of vasculitis were found to be the best predictors of IHD over the followup in patients with GCA. Both age and hypertension are known to be risk factors for the development of cardiovascular complications. However, the presence of an abnormal temporal artery as a feature associated with a lower risk of IHD in GCA is difficult to explain. As described, our patients with GCA were uniformly treated and there were no significant differences between the living and the deceased patients with respect to mean initial and cumulative doses of prednisone after one year of treatment[23]. The presence of an abnormal temporal artery on physical examination at diagnosis of GCA did not account for any specific individualized therapeutic approach. However, there is no evidence that inflammation disappears as quickly as the symptoms once steroid therapy is started. Experimental studies using SCID mice have confirmed that the disease persists subclinically despite chronic treatment[24].

Despite limitations due to the retrospective design of our study, our observations suggest that the incidence of ischemic heart disease is not as high as reported in Northern Sweden. Elderly patients with GCA should be monitored for the development of IHD, in particular those with hypertension at the time of diagnosis.

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