Geographical and Genetic Factors Do Not Account for Significant Differences in the Clinical Spectrum of Giant Cell Arteritis in Southern Europe

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ABSTRACT. ***Objective.*** To investigate whether genetic and geographical differences may influence the clinical spectrum of giant cell arteritis (GCA), we compared the demographic and clinical features of patients with biopsy-proven GCA from Reggio Emilia (Northern Italy) and Lugo (Northwest Spain) during a 15-year period.

Methods. We performed a retrospective review of the case records of all patients diagnosed with biopsy-proven GCA at Hospital Xeral-Calde (Lugo, Spain) and Hospital Santa Maria Nuova (Reggio Emilia, Italy) between 1 January 1986 and 31 December 2001. Both hospitals are the only referral centers for populations living in central Galicia and central Emilia Romagna, respectively.

Results. During the period of study, 194 Lugo residents and 126 Reggio Emilia residents were diagnosed with biopsy proven GCA. Reggio Emilia patients were more likely to be female (74% vs 54%; p = 0.0001). Although Lugo patients complained of headache (86%) more commonly than did those from Reggio Emilia (77%), the difference was only marginally significant (p = 0.05). The proportion of patients with visual manifestations or visual loss was remarkably similar (22% for visual manifestations and 17% for visual loss in Lugo and 29% and 21% for Reggio Emilia residents). The mean erythrocyte sedimentation rate prior to the onset of therapy was also similar.

Conclusion. Apart from differences in sex, the clinical spectrum of GCA in these 2 Southern European regions was similar. (J Rheumatol 2004;31:520–3)

Key Indexing Terms:
GIANT CELL ARTERITIS TEMPORAL ARTERY BIOPSY LUGO REGGIO EMILIA

Giant cell arteritis (GCA) is an inflammatory vasculopathy that usually involves large and medium-sized blood vessels with predisposition for the involvement of the branches of the carotid artery[1]. It is the most common vasculitis in Western countries, in particular in people older than 50 years of age with Northern European ancestry[2-4]. In these populations annual incidence rates are generally higher than 20/100,000 people per population 50 years and older. In Southern Europe and Israel, in contrast, the incidence is lower than 11/100,000 people per population 50 years and older[5-7]

Genetic, geographic, and environmental factors have been implicated in the susceptibility to GCA[8]. The genetic contribution to the susceptibility to GCA was suggested by reports that showed cases of GCA among first-degree relatives. The implication of MHC class II-molecules in the susceptibility to GCA has been widely described[9]. Geographical factors have also been implicated in the differences in the incidence of GCA. A significant trend to increasing incidence with more northerly latitude has been noted[8].

GCA has been extensively studied in Lugo, Northwest Spain, and Reggio Emilia, Northern Italy. In these 2 Southern European populations the incidence of GCA is different. While in Lugo the annual incidence rate for GCA is 10.2 per 100,000 population 50 years and older[5], the incidence in Reggio Emilia is much lower, 6.9 per 100,000 population 50 years and older[6]. Interestingly, GCA susceptibility in both populations also shows important immunogenetic differences[9]. In this regard, GCA in Lugo is associated with HLA-DRB1*04 alleles[10]. However, this is not the case for Reggio Emilia patients[11]. Differences between both populations in terms of the potential association of this vasculitis with other non-HLA alleles have also been described[12,13].

To further investigate this common vasculitis in the elderly, we assessed whether geographical differences along

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with a different genetic background of these 2 European populations may account for a different clinical spectrum of the disease.

MATERIALS AND METHODS

We performed a retrospective review of the case records of all patients diagnosed with biopsy-proven GCA at Hospital Xeral-Calde (Lugo, Spain) and Hospital Santa Maria Nuova (Reggio Emilia, Italy) between 1 January 1986 and 31 December 2001. Hospital Xeral-Calde is the referral center for a well-defined population of almost 250,000 people living in the middle of the province of Lugo, in Northwest Spain[5,10]. Hospital Santa Maria Nuova is also the only referral center for population of 462,860 people living in central Emilia Romagna[6].

Inclusion criteria. For the purpose of this study only patients with biopsy-proven GCA were included. We considered both in-patients and out-patients. Patients were diagnosed as having biopsy-proven GCA if the histological examination of the temporal artery biopsy (TAB) showed disruption of the internal elastic laminae with infiltration of mononuclear cells into the arterial wall with or without giant cells[5]. Although the populations of Lugo and Reggio Emilia are stable and no important migration has occurred in these areas during the last 2 decades[5], residency in Lugo or Reggio Emilia for at least one year prior to diagnosis with GCA was required to avoid migration bias.

Temporal artery biopsy (TAB) procedure. TAB procedure in Lugo and Reggio Emilia has been described[5,6,14]. In both populations a TAB was routinely performed in all patients with clinical manifestations of GCA. The side with predominant local temporal symptoms and signs was selected for biopsy. Segments longer than 2 cm were generally obtained. Also, in both regions, biopsies were performed in those patients with clinically isolated polymyalgia rheumatica (PMR), without any vascular manifestation of GCA, if they had systemic signs/symptoms.

Data collection. Besides demographic features and erythrocyte sedimentation rate (ESR) prior to the onset of the steroid therapy, the following clinical data at the time of diagnosis were assessed: headache, abnormal temporal arteries on physical examination, scalp tenderness, jaw claudication, visual manifestations (transient visual loss including amaurosis fugax, permanent visual loss, and diplopia), systemic signs/symptoms (asthenia, anorexia and weight loss of at least 4 kg or fever greater than 38°C), and PMR (marked aching and stiffness bilaterally without other apparent cause in at least 2 of 3 regions; namely: neck, shoulder girdle, or hip girdle).

In both populations all GCA patients with cranial ischemic or other vascular manifestations were initially treated with 40-60 mg of prednisone day. Some patients with visual ischemic manifestations were also treated with intravenous pulses of methylprednisolone (1 g daily for 3 consecutive days). Patients without evident vascular involvement who presented with PMR manifestations received an initial dose of prednisone between 10 and 20 mg/day. In these patients prednisone dose was increased to 40 mg/day as soon as information about a positive TAB was available.

Statistical analysis. Continuous data were described as mean and standard deviation (mean ± SD), and categorical variables as percentage. Comparisons between 2 categories were made using Student's t test (2 tailed) for continuous variables. To analyze categorical data we performed the chi square test. When the minimum expected value was less than 5, Fisher's exact test was used. Statistical significance was defined as $p < 0.05$.

RESULTS

During the period of study, 194 Lugo residents and 126 Reggio Emilia residents were diagnosed with biopsy proven GCA. Table 1 shows the demographic characteristics and clinical manifestations at diagnosis in both regions.

Although in both populations biopsy-proven GCA was more common in women, the proportion of men diagnosed with GCA was significantly higher in Lugo (45.9%) than in Reggio Emilia (26.2%) ($p = 0.0001$).

In both populations the mean age at the time of diagnosis was strikingly similar (75 years in Lugo and 74 in Reggio Emilia). Lugo patients complained of new onset of headache (86%), more commonly than did those from Reggio Emilia (77%). However, the difference was only marginally significant ($p = 0.05$). Despite having geographical and genetic differences the proportion of patients with visual manifestations or visual loss was remarkably similar (22% for visual manifestations and 17% for visual loss in Lugo and 29% and 21% for Reggio Emilia residents, respectively).

Other cranial ischemic manifestations exhibited similar prevalence in both populations (Table 1). It was also the case for PMR in the setting of biopsy-proven GCA (41% in both populations). Finally, the mean ESR prior to the onset of therapy, as the classical marker of inflammatory response, yielded remarkable similarities between both populations (93 mm/h in Lugo and 92 mm/h in Reggio Emilia).

DISCUSSION

The different ethnic origins of the European populations may explain the differences observed in the genetic studies on GCA in Lugo and Reggio Emilia[9-13]. Also, geographical differences may play a role in the different incidence of the disease in both populations[5,6]. They may imply different pathogenic mechanisms for the development of GCA. However, when demographic and clinical features were compared, apart from gender, no important clinical differences between both populations were observed. In both regions GCA occurred in people in their middle seventies and the frequency of PMR manifestations and systemic symptoms as well as the ESR values were remarkably similar. Of particular interest, in these 2 populations there was no difference in the prevalence of visual loss. Of note, in both regions the proportion of patients with visual ischemic manifestations and blindness was similar to that described by Machado, *et al* in Olmsted County, Minnesota, during the period 1950-1985[15].

In Table 2 demographic and clinical findings of GCA patients in other geographic areas are shown[2,15-22]. Differences in the design of these studies and in case selection might account for some differences. However, as a whole, the overall clinical spectrum of the disease at diagnosis was similar in the different geographical areas.

A question unanswered for rheumatologists from Lugo was the higher frequency of GCA in men in Lugo compared with the rest of series[8]. It was mainly due to the predominance of GCA in men during the period 1981-1990[23]. This fact could not be explained by sex differences in the structure of the population. However, although a progressive increase of the incidence in both genders was found over the

Table 1. Demographic and clinical differences between patients with biopsy-proven GCA diagnosed in 2 different populations from Southern Europe (Lugo, Northwest Spain, and Reggio Emilia, Northern Italy) during the period 1986–2001. Results are expressed as mean ± SD unless otherwise indicated.

Variables	GCA Patients from Lugo n = 194	GCA Patients from Reggio Emilia n = 126	p
Males/females, n (%)	89/105 (45.9/54.1)	33/93 (26.2/73.8)	0.0001
Age at onset of disease, (yrs)	74.9 ± 6.8	73.5 ± 6.9	NS
Duration of symptoms before diagnosis, wks	10.6 ± 11.8	10.7 ± 7.9	NS
Headache (%)	167 (86.1)	97 (77.0)	0.05
Abnormalities of temporal arteries on physical examination (%)	144 (74.2)	79 (65.3)	NS
Scalp tenderness (%)	71 (36.6)	47 (38.8)	NS
Jaw claudication (%)	80 (41.2)	55 (43.7)	NS
Visual manifestations (%)	42 (21.6)	37 (29.4)	NS
Visual loss* (%)	32 (16.5)	26 (20.6)	NS
Systemic signs/symptoms** (%)	130 (67.0)	88 (69.8)	NS
Polymyalgia rheumatica (%)	79 (40.7)	52 (41.3)	NS
Erythrocyte sedimentation rate, mm/1st h	92.7 ± 22.2	92.2 ± 30.7	NS

* Permanent and temporary. ** Asthenia, anorexia, and weight loss of at least 4 kg and/or fever greater than 38°C.

Table 2. Demographic and clinical findings of patients with giant cell arteritis in different geographic areas*.

Variables	Norway[16], Vest Agder County n = 53	Norway[17], Aust Agder County** n = 39	Iceland[2] n = 133	Sweden[18,19] n = 41	France[§20] n = 207	Israel[§§21] n = 30	USA[15], Olmsted County n = 94	Japan[22], n = 66
Female/males, %	72/28	74/26	71/29	67/33	76/24	47/53	83/17	64/36
Mean age at diagnosis, yrs	72.7	70.4	71.9	NR	NR	74.0	NR	72.5
Headache, %	70	85	63	97	83	87	77	58
Abnormalities of temporal arteries on physical examination, %	47	NR	44	39	61	NR	53	59
Scalp tenderness, %	4	NR	8	10	NR	3	47	40
Claudication (jaw and/or tongue and/or deglutition) %	13	28	11	20	41	13	51	6
Visual symptoms, %	19	18	14	8[&&]	32	40	18	36
Systemic signs/symptoms*, %	57	43***	74[&]	32	91	73[#]	48	44
Polymyalgia rheumatica, %	53	—	48	NR	40	27	34	28

* Asthenia, anorexia, weight loss, and/or fever; ** only patients with GCA alone considered; *** they were evaluated separately, fever, reported here, was the most frequent; [&] only general fatigue recorded; [&&] only permanent loss of vision recorded; [§] only patients with biopsy-positive GCA considered; [§§] only patients with biopsy-proven GCA considered; [#] only fever recorded; NR: not reported.

last 2 decades, in recent years there has been a trend towards a higher increase in women. Thus, during the period 1992-2001, 85 (59%) of the 144 patients diagnosed with biopsy-proven GCA in Lugo were women. Due to this, it is possible that gender differences may no longer be observed in future comparative studies between both populations.

In conclusion, our data add evidence that regardless of genetic and geographical factors, the clinical spectrum of biopsy-proven GCA remains constant in different parts of Southern Europe.

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