Comparison of biopsy-proven giant cell arteritis in North America and Southern Europe: a population-based study

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ABSTRACT

Objective. To compare clinical characteristics, treatment and prognosis of two population-based cohorts of patients with biopsy-proven giant cell arteritis (GCA) from Olmsted County, Minnesota, USA (Olmsted cohort) and the Reggio Emilia area, Northern Italy (Reggio cohort).

Methods. All patients residing in Olmsted County and the Reggio Emilia area with a new diagnosis of biopsy-proven GCA in 1986-2007 were retrospectively identified. Patients were followed from GCA diagnosis to death, migration or September 2011.

Results. The study included 110 patients in the Olmsted and 144 in the Reggio cohort. Compared with the Olmsted cohort, patients from the Reggio cohort had longer duration of symptoms prior to diagnosis (median 1.4 months vs. 0.7, p<0.001) and were younger (mean 74.6 years vs. 77.8, p=0.002), more likely to have cranial symptoms (93% vs. 86%, p=0.048), permanent vision loss (21% vs. 6%, p=0.001) and systemic symptoms (67% vs. 46%, p=0.001). ESR and CRP were higher (mean 88 mm/h vs. 67, and 89.0 mg/L vs. 35.2, both p<0.001) in the Reggio cohort. Patients from the Olmsted cohort received a higher initial prednisone dose (mean 53.6 mg/day vs. 49.5, p=0.001). There were no differences in relapse rates, cumulative glucocorticoid (GC) dosages at 1, 2 and 5 years, and time to first GC discontinuation.

Conclusion. Geographical, genetic and/or environmental factors may contribute to the different clinical features at onset of GCA observed in this study.

Introduction

Giant cell arteritis (GCA) is an inflammatory vasculopathy that involves large and medium-sized arteries, mainly the thoracic aorta and its branches, and may produce a wide spectrum of clinical symptoms. It is the most common systemic vasculitis in Western countries in individuals older than 50 years. Epidemiologic studies have shown that incidence rates increase with age and are higher in populations of Northern European origin compared with those of Mediterranean countries. Although its aetiology is unknown, genetic, geographical, and environmental factors have been implicated in the susceptibility to GCA (1, 2). The strong contribution of the HLA class II region to GCA susceptibility has been shown in a recent large-scale genetic analysis of subjects from six different countries of European ancestry (3). Most population-based studies have found that life expectancy of patients with GCA is comparable to that of the general population, while few studies have demonstrated an increased mortality (4).

To date, only one study compared the clinical spectrum of GCA in two population-based cohorts of patients with biopsy-proven GCA from Southern Europe (Lugo, Spain vs. Reggio Emilia, Italy) (5). The overall clinical spectrum of the disease at diagnosis was similar in these two different geographical areas, and the authors concluded that genetic and environmental factors did not seem to influence the clinical presentation of GCA in Southern Europe. To date, there has been no systematic comparison of the clinical features, treatment course and outcomes of patients with GCA from different geographical areas and with different ethnic background. GCA has been extensively studied in Olmsted County, Minnesota, where the population is composed primarily of Northern European descent, and Reggio Emilia, Northern Italy, a Mediterranean country. In these two populations, the incidence of GCA was highly different.
The overall age- and sex-adjusted incidence of GCA per 100,000 persons 50 years of age or older was 18.8 in Olmsted County, and 5.8 in Reggio Emilia area (6, 7). GCA susceptibility showed important immunogenetic differences. GCA was associated with HLA-DRB1*04 alleles in Olmsted County but not in Reggio Emilia (8-10). Life expectancy of patients with GCA was comparable to that of the general population in these two areas (7, 11).

The aim of this study is to compare clinical characteristics, treatment, and outcomes of two population-based cohorts of patients with biopsy-proven GCA from Olmsted County, Minnesota, (Olmsted cohort) and the Reggio Emilia area, Northern Italy (Reggio cohort).

Methods
In this retrospective population-based cohort study, all patients with incident biopsy-positive GCA diagnosed over a 21-year period (from January 1, 1986 to December 31, 2007) living respectively in Olmsted County and the Reggio Emilia area were included. The Rochester Epidemiology Project is a unique record-linkage system whose database allows access to all inpatient and outpatient medical records from all healthcare providers for the population of Olmsted County. This resource is well-suited for population-based epidemiologic studies (12). The Reggio Emilia Hospital (Arcispedale Santa Maria Nuova) is the only referral centre for the population of 519,480 people living in the Reggio Emilia area. All patients referred by medical practitioners and community-based specialists for suspected GCA are assessed and followed by rheumatologists at the Reggio Emilia Hospital. The computerised files of the Pathology Unit of this hospital include records of all temporal artery biopsies (TABs) performed in the Reggio Emilia area from January 1, 1986. In a previous epidemiologic study, we have described the system used, which ensures a virtually complete ascertainment of all biopsy-positive cases of GCA among the Reggio Emilia area residents (7).

For this study, all patients residing in Olmsted County and the Reggio Emilia area who underwent TAB between January 1, 1986, and December 31, 2007 were identified and histopathology reports were reviewed. Patients were diagnosed as having biopsy-proven GCA and included in the study if TAB showed transmural infiltration of mononuclear cells in the arterial wall with or without giant cells. All inpatient and outpatient medical records of the included patients were reviewed from the date of GCA diagnosis to the end of the study follow-up (30th September 2011), last visit, migration or death. Only patients who were followed for at least 6 months after GCA diagnosis were considered for the treatment and relapse analysis. Data abstracted included demographics, cardiovascular risk factors (hypertension, hypercholesterolaemia, smoking (current/ever), diabetes mellitus), and previous diagnosis of polymyalgia rheumatica (PMR). Clinical features, laboratory and histology findings, medical treatment and disease outcomes were also abstracted. Relapse was defined as the reappearance of symptoms of GCA or PMR and/or an increase in ESR and/or CRP that required an increase in glucocorticoid (GC) therapy.

The study was approved by the Institutional Review Boards at Mayo Clinic and Olmsted Medical Center and the Reggio Emilia Provincial Ethics Committee, and all participants gave written informed consent.

Statistical analysis
Continuous data were presented as mean (SD) or median (interquartile range (IQR) (Q1, Q3)) and categorical variables as percentage. Characteristics were compared between cohorts using Wilcoxon rank sum and chi-square tests. Relapse rates were calculated using person-year methods and differences in relapse rates between the cohorts were computed assuming the relapse rates followed a Poisson distribution. Analyses were performed using SAS v. 9.4 (SAS Institute) and R 3.4.2 (R Foundation for Statistical Computing).

Results
During the study period, 110 patients with biopsy-proven GCA were included in the Olmsted cohort and 144 in the Reggio cohort. Baseline demographic, clinical manifestations and laboratory findings of the two study cohorts are presented in Table I.

Table I. Baseline demographic, clinical manifestations and laboratory findings of the two study cohorts*.

<table>
<thead>
<tr>
<th></th>
<th>Olmsted (n=110)</th>
<th>Reggio (n=144)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age at diagnosis (SD) years</td>
<td>77.8 (7.6)</td>
<td>74.6 (7.4)</td>
<td>0.002</td>
</tr>
<tr>
<td>Female</td>
<td>88/110 (80%)</td>
<td>118/144 (81.9%)</td>
<td>0.695</td>
</tr>
<tr>
<td>Current smoker</td>
<td>7/90 (7.8%)</td>
<td>23/131 (17.6%)</td>
<td>0.037</td>
</tr>
<tr>
<td>Diabetes</td>
<td>5/110 (4.5%)</td>
<td>6/124 (4.8%)</td>
<td>0.916</td>
</tr>
<tr>
<td>Hypertension</td>
<td>64/110 (58.2%)</td>
<td>81/122 (66.4%)</td>
<td>0.197</td>
</tr>
<tr>
<td>Hypercholesterolaemia</td>
<td>59/110 (53.6%)</td>
<td>16/128 (12.5%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Time from symptoms onset to TAB (Q1, Q3) months</td>
<td>0.7 (0.2, 1.3)</td>
<td>1.4 (1.0, 2.7)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

*Except where indicated otherwise, values are the number of patients who were positive/number of patients for whom data were available (%).
**At least one of the following: fatigue, anorexia, weight loss of at least 4 Kg, or fever.
findings for the two study cohorts are reported in Table I. Compared with the Olmsted cohort, patients from the Reggio cohort were younger, had longer duration of symptoms prior to diagnosis and were more frequently current smokers. Reggio patients were more likely to have cranial symptoms, temporal artery abnormalities on physical examination, partial or complete unilateral or bilateral permanent vision loss, systemic symptoms and PMR at or before GCA diagnosis. Hypercholesterolaemia and scalp tenderness were more common in the Olmsted cohort. ESR and CRP levels were higher and haemoglobin lower in Reggio than in the Olmsted cohort. The median duration of follow-up was 6.8 years for the Olmsted cohort and 5.9 years for the Reggio cohort. Treatment and outcome variables for the two study cohorts are reported in Table II. Patients from the Olmsted cohort received a higher initial prednisone dose. There were no differences in relapse rates, cumulative GC dosages at 1, 2 and 5 years, time to first GC discontinuation and time to reach a sustained (for at least 6 months) GC discontinuation (Fig. 1). However, the Reggio cohort reached a prednisone dose <10 mg/day sooner and had a first relapse later than the Olmsted cohort (Fig. 2).

Discussion
To our knowledge, this is the first study comparing clinical characteristics, treatment, and outcomes of two population-based cohorts of patients with biopsy-proven GCA from different geographical areas. Compared with the Olmsted cohort (where the population is composed primarily of people of Northern European ancestry), patients from the Reggio cohort (Mediterranean area) were younger, more likely to have permanent vision loss, systemic symptoms and PMR. ESR and CRP at diagnosis were higher and haemoglobin lower in Reggio than in the Olmsted cohort, reflecting a more intense inflammatory reaction in Reggio Emilia patients with GCA. There were no differences in relapse rates and cumulative GC dosages.

A significant difference in age at GCA diagnosis was found in the present study.

Epidemiologic studies have shown that GCA incidence rates increase with age, peaking in the 70–79 years age group (2). In a recent population-based study from the Reggio Emilia area, Catanoso et al. did not find an increase in the age at onset of GCA during a 26-year period (1986-2012). Mean age at incidence of GCA was 73.7 years in the first decade of the study (1986-1995) compared to 73.5 in the last decade (2003-2012) (7). Different results were reported by Kermani et al. in a population-based study from the Olmsted County over a 55-year period (1950-2004). The mean age at incidence of GCA significantly increased from 73.2 years for cases diagnosed between 1950 and 1979, to 76.7 years for incident cases diagnosed between 1980 and 2004. The increase in age at diagnosis was related to an increase in the incidence of GCA in patients >70 years. This observation was not entirely explained by demographic changes observed during the study period (13).

Although different time intervals were analysed in the 2 studies, the mean age at GCA diagnosis in the Reggio Emilia population remained stable over time, and it was similar to that observed in the first study period in Olmsted County population. In most of the studies, the age at diagnosis remained stable over time. Only one study from Lugo, Spain, showed a trend for a gradual increase in the age at GCA diagnosis in the first period of the study (14). Interaction of different genetic and environmental factors with the ageing immune system of individuals from different geographic area could explain the different age at diagnosis found in the present study.

In the present study, patients from the Reggio cohort had a higher frequency of permanent vision loss compared with those from the Olmsted cohort, while there were no differences in the prevalence of amaurosis fugax and diplopia. The significant delay in the diagnosis of GCA in the Reggio cohort could (at least partly) explain this finding.

Vision loss is one of the most feared

Table II. Comparison of treatment and outcome variables in the Olmsted and Reggio cohorts.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Olmsted (n=110)</th>
<th>Reggio (n=144)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Initial prednisone dose mean (SD) mg</td>
<td>53.6 (15.3)</td>
<td>49.5 (12.8)</td>
<td>0.001</td>
</tr>
<tr>
<td>Follow-up median (Q1, Q3) years</td>
<td>6.8 (3.7, 11.0)</td>
<td>5.9 (2.8, 8.8)</td>
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</tr>
<tr>
<td>Relapse rate per year median (Q1, Q3)</td>
<td>0.3 (0.1, 0.5)</td>
<td>0.2 (0.0, 0.6)</td>
<td>0.355</td>
</tr>
<tr>
<td>Time to first relapse KM* median (Q1, Q3) months</td>
<td>7.9 (6.3, 10.1)</td>
<td>13.6 (11.5, 19.2)</td>
<td>0.003</td>
</tr>
</tbody>
</table>

Cumulative prednisone dose at 1 year mean (SD) g

<table>
<thead>
<tr>
<th>Variable</th>
<th>Olmsted (n=110)</th>
<th>Reggio (n=144)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cumulative prednisone dose at 2 year mean (SD) g</td>
<td>6.7 (2.7)</td>
<td>6.7 (2.6)</td>
<td>0.951</td>
</tr>
<tr>
<td>Time to prednisone &lt;10mg KM* median (95% CI) months</td>
<td>9.0 (3.8)</td>
<td>8.6 (4.3)</td>
<td>0.189</td>
</tr>
<tr>
<td>Time to prednisone discontinuation KM* median (95% CI) months</td>
<td>7.9 (6.2, 10.1)</td>
<td>4.9 (3.9, 5.9)</td>
<td>0.012</td>
</tr>
</tbody>
</table>

KM: Kaplan-Meier; CI: confidence interval.

Fig. 1. Percent of patients who discontinued steroids for at least 6 months by disease duration. Log-rank p-value = 0.350.

Fig. 2. Time to first relapse. Log-rank p-value = 0.003.
cranial ischaemic complications of GCA. This clinical manifestation is typically an early event in the disease course, appearing before diagnosis and GC treatment, and is generally irreversible. Transient visual manifestations (such as amaurosis fugax and diplopia) can precede permanent visual loss by hours or days. GCs are effective in preventing vision loss, but can rarely revert established blindness. Adequate doses of GCs should therefore be immediately prescribed to all patients with suspected GCA (15, 16).

A decrease in the frequencies of permanent vision loss have been recently reported from different geographical areas, suggesting a favourable effect of earlier diagnosis and treatment (17-19). In a population-based study from the Olmsted County over a 55-year period, incidence of visual manifestations and permanent vision loss decreased respectively from 25% and 9.8% in patients diagnosed in 1950-1979 to 11% and 2% in 1980-2004. However, no significant delay in the diagnosis of GCA was noted in patients with visual manifestations compared to those without (17).

Factors other than diagnosis delay could have contributed to the different prevalence of vision loss found in the two cohorts. Although the initial prednisone dose was lower and its tapering was faster in the Reggio cohort, all patients developed visual loss before GCs. We can therefore exclude that the observed differences in the GC schedule contributed to the observed differences in visual loss. Several previous studies, including one from the Reggio Emilia area, showed that GCA patients with a lower inflammatory response had a higher risk of developing ischaemic manifestations, suggesting a protective role against ischaemic events of higher interleukin-6 levels through its angiogenic activity in patients with a strong acute-phase response (20-28). Patients from the Reggio cohort had a more intense inflammatory response but more frequent vision loss than those from the Olmsted cohort; therefore, a more intense inflammatory response was not able to protect Reggio Emilia patients from blindness.

We did not find any differences in the prevalence of the other known risk factors for vision loss in GCA (previous cranial ischaemic event, jaw claudication, hypertension) (15). Genetic variations may modulate the risk of vision loss in GCA and contribute to the results of the present study. A large-scale genetic analysis has recently confirmed a strong contribution of the HLA class II region to GCA susceptibility, and an association of HLA-class II DRB1*04 with visual complications has been described (3, 22). However, the association of HLA-DRB1*04 with GCA has been observed in different Caucasian populations, including in Olmsted County, but not in Reggio Emilia (8-10).

Several single nucleotide polymorphism risk signals in loci among non-HLA regions have also been associated with visual manifestations (15). To this regard, a study from Reggio Emilia reported an association between vision loss and homozygosity for the PLA2 allele of the PLA1/A2 polymorphism of ITGB3 (29). PLA2 allele is linked to increased platelet adhesion and aggregation, and could have a role in inducing the ischaemic manifestation in GCA. However, this study has not been replicated in other populations (including the Olmsted population) and will require validation in larger patient cohorts.

Compared to the Olmsted cohort, a more intense inflammatory response characterised by more frequent systemic symptoms, higher ESR and CRP and lower haemoglobin levels was found in patients from the Reggio cohort. The delay in the diagnosis of GCA in the Reggio cohort, with the related possibility to have an increased inflammatory response, could partially explain these findings. In comparison to the Olmsted cohort, we observed a higher prevalence of PMR in the Reggio cohort, prevalence that was similar to that observed in other population-based studies (1, 2, 5). The reason could be related to the fact that all patients were evaluated by a rheumatologist who searched for PMR manifestations in the Reggio cohort but not in the Olmste cohort.

Disease relapses have been reported in 34 to 74.5% of GCA patients in observational studies from different geographical areas. These differences were related to the different study design (prospective vs. retrospective) and definition of relapse used (30). In two retrospective, population-based studies from the Reggio Emilia area and the Olmsted County, the frequencies of disease relapse during GC tapering were 36.5% and 74.5%, respectively (30, 31). In the present study, relapse was uniformly defined as the reappearance of symptoms of GCA or PMR and/or an increase in ESR and/or CRP that required an increase in the GC therapy. We did not find differences in relapse rates, confirming that the differences in the previous studies were mainly related to the different definition of relapse and not due to different disease severity. Even if patients from the Olmsted cohort received a higher initial prednisone dose, we did not find differences in the cumulative GC dosages at 1, 2 and 5 years, time to first GC discontinuation and time to reach a sustained GC discontinuation. However, the Olmsted cohort reached a prednisone dose <10 mg/day later and had a first relapse sooner than the Reggio cohort.

Our study has a number of strengths and limitations. The population-based design, the inclusion of patients with fully established diagnosis using TAB as the gold standard, the large size of the patient cohorts followed at two tertiary care centres and the long duration of follow-up are notable strengths of our study and support the reliability of our results. Retrospective data retrieval was the main limitation of the study.

In conclusion, patients with GCA in this Italian population from Reggio Emilia were younger, more likely to have cranial symptoms, permanent vision loss and tended to have a higher burden of inflammation than those from the US population from Olmsted County. Overall, GC use during the disease course was similar in both cohorts. Geographical, genetic and/or environmental factors may contribute to the different clinical features at onset of GCA observed in this study, which will require further validation.
References


