Risk factors for severe cranial ischaemic events in an Italian population-based cohort of patients with giant cell arteritis

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Objective. To evaluate the impact of traditional cardiovascular risk factors, carotid atherosclerosis and the effect of anti-platelet/anti-coagulant therapy on the occurrence of severe cranial ischaemic events (CIEs) in GCA.

Methods. We identified 180 Reggio Emilia (Italy) residents with biopsy-proven GCA diagnosed between 1986 and 2005. We evaluated data on demographics, clinical features, laboratory investigations, cardiovascular risk factors, anti-platelet/anti-coagulant use and carotid atherosclerosis.

Results. Systemic signs/symptoms were significantly less frequent (P = 0.004) and ESR and C-reactive protein (CRP) values at diagnosis were significantly lower (P = 0.03 and P = 0.04, respectively) in patients with CIEs. The prevalence of hypertension and ischaemic heart disease was significantly higher in patients with CIEs than in those without (P = 0.01 and P = 0.006, respectively). Patients treated with anti-platelet/anti-coagulant therapy were significantly more likely to suffer CIEs than those without (P = 0.03), while CIEs were significantly associated with ischaemic heart disease in this subset of patients (P = 0.02). By multivariate logistic regression, we found that the best predictors for the development of severe CIEs included the absence of high (>5.38 mg/dl) CRP levels at diagnosis (OR = 0.31, 95% CI 0.08, 1.20), the absence of systemic manifestations (OR = 0.30, 95% CI 0.08, 1.08), the presence of hypertension (OR = 7.77, 95% CI 0.83, 72.76), and a past history of ischaemic heart disease (OR = 8.65, 95% CI 0.92, 80.95).

Conclusions. In GCA, hypertension, a past history of ischaemic heart disease and a low inflammatory response are associated with a higher risk of developing severe CIEs.

Key words: Giant cell arteritis, Cranial ischaemic events, Cardiovascular risk factors, Carotid atherosclerosis, Population-based study.

Introduction

GCA-related severe cranial ischaemic events (CIEs) include vision loss and the less common cerebrovascular accidents (CVAs) (stroke and/or transient ischaemic attack). These events may cause irreversible damage. Permanent partial or complete loss of vision in one or both eyes occurs in up to 20% of the patients with GCA and is often an early manifestation of the disease [1, 2]. CVA may occur at the time of GCA diagnosis, in which case they are considered attributable to the GCA inflammatory process [3-6]. In the clinical series described by Gonzalez-Gay et al. [3], 2.4% of 210 patients with GCA developed CVA between the onset of symptoms of GCA and 1 month after the onset of steroid therapy [3].

Because the prognosis of GCA is related to the development of severe CIEs, it is important to identify those patients at risk of developing these complications. A more aggressive therapy with higher doses of prednisone may prove beneficial in these patients. Some studies have evaluated the possible influence of traditional risk factors of atherosclerosis on the development of severe ischaemic complications of GCA; however, the results were controversial [3-5, 7]. The goal of our study was to evaluate the impact of traditional cardiovascular risk factors, carotid atherosclerosis assessed by ultrasonography, past history of ischaemic cerebrovascular events and ischaemic heart disease, and the effect of anti-platelet or anti-coagulant therapy on the occurrence of severe CIEs in a large population-based incident cohort of patients with biopsy-proven GCA.

Patients and methods

Patients

We reviewed the computerized Pathology laboratory’s register, which keeps records of all temporal artery biopsies performed in Reggio Emilia (Italy) at Santa Maria Nuova Hospital between 1986 and 2005. The positive specimens were reviewed by a pathologist and 180 patients residing in the Reggio Emilia area were identified. Santa Maria Nuova Hospital is the only referral centre for a population of 462 860 people living in central Emilia Romagna. The Ethical Committee approved the study and informed consent was obtained from patients before inclusion in the study.

Patients were diagnosed as having biopsy-proven GCA if histological examination of 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. Temporal artery biopsy procedures in Reggio Emilia have been described previously [8, 9]. Temporal artery biopsy was routinely performed in all patients with clinical manifestations of GCA. Segments >2 cm were generally obtained.

All inpatient and outpatient medical records of these 180 patients were reviewed. Besides demographic features, the following clinical data at the time of diagnosis were evaluated: headache, abnormal temporal arteries on physical examination, scalp tenderness, jaw claudication, visual manifestations (transient visual loss including amaurosis fugax, permanent visual loss and diplopia), CVAs (stroke and/or transient ischaemic attacks), aortic arch syndrome, systemic signs/symptoms (anorexia and weight loss of at least 4 kg or fever) and PMR defined as marked bilateral aching and stiffness without other apparent cause in at least two of the three regions, namely shoulder girdle, hip girdle or neck.

Visual loss and CVAs were considered CIEs and attributed to GCA if they occurred within the time between the onset of GCA symptoms/signs and 1 month after the onset of corticosteroid therapy.
Information on traditional risk factors for atherosclerosis (hypertension, hypercholesterolaemia, hypertriglyceridaemia, diabetes and smoking history), carotid atherosclerosis, ischaemic heart disease, CVA preceding the onset of GCA and medications taken by the patients was obtained from in- and outpatient medical records as well as by patients’ interviews whenever required.

The vast majority of patients included in this study had been admitted to the hospital with a clinical suspicion of GCA, allowing us to accurately evaluate these variables. Furthermore, we reviewed all the notes of family physicians, hospital- and community- based specialists, and all the charts and discharge summaries of the hospitalizations which preceded GCA diagnosis.

Traditional cardiovascular risk factors were defined according to standardized diagnostic criteria. Cigarette smokers were classified as heavy smokers (patients who still smoked at the time of GCA diagnosis or who had been smoking within the 10 yrs before the onset of GCA symptoms) and non-smokers or previous smokers (never smoked or quit smoking at least 10 yrs before the disease onset) [3].

Subjects with two or more blood pressure readings >140 mmHg systolic and/or 90 mmHg diastolic were considered to be hypertensive [10, 11]. Patients were also considered to have hypertension if they had a physician’s diagnosis of hypertension in their medical records and/or were receiving anti-hypertensive treatment with specific lipid-lowering drugs [12, 13].

Subjects with two or more blood pressure readings >140 mmHg systolic and/or 90 mmHg diastolic were considered to be hypertensive (OR 5.38, 95% CI 0.83, 36.21; P = 0.02). The absence of systemic manifestations (OR 0.30, 95% CI 0.08, 1.08) and the presence of hypertension (OR 7.77, 95% CI 0.83, 72.76) and a past history of ischaemic heart disease (OR 8.65, 95% CI 0.92, 80.95) (Table 2). However, only a statistical trend was observed for these variables.

The diagnosis of carotid atherosclerosis was based on carotid ultrasonography before disease onset. The following laboratory parameters evaluated prior to the onset of steroid therapy were considered: ESR determined using the Westergren method (because most of our patients were females over the age of 50 yrs, the upper limit of normal was defined by the documentation of a characteristic ECG or a recorded physician’s diagnosis in a patient with no documented history of MI.

The diagnosis of ischaemic heart disease was based on a past history positive for at least one of the following [16]: myocardial infarction (MI), silent MI, revascularization procedures and a clinical diagnosis of angina pectoris. Silent MI was defined by the documentation of a characteristic ECG or a recorded physician’s diagnosis in a patient with no documented history of MI.

The following laboratory parameters evaluated prior to the onset of steroid therapy were considered: ESR determined using the Westergren method (because most of our patients were females over the age of 50 yrs, the upper limit of normal reference range considered for ESR was 30 mm/1st h) and C-reactive protein (CRP) measured by nephelometry (NA latex CRP kit, Behringwerke, Marburg, Germany; upper limit of the normal reference range was 0.5 mg/dl).

Of the 25 patients taking anti-platelet or anti-coagulant therapy, 17 (68%) had a negative past history of ischaemic heart disease, while 8 (32%) had a positive history. The frequency of severe CIEs was significantly higher in the patients with history of ischaemic heart disease compared with those without (75 vs 23.5%, respectively, P = 0.02).

The frequency of severe CIEs was significantly higher in the patients with history of ischaemic heart disease compared with those without (75 vs 23.5%, respectively, P = 0.02). Multivariate logistic regression revealed that the best predictors for the development of severe CIEs included the absence of high CRP levels at diagnosis (>5.38 mg/dl: OR = 0.31, 95% CI 0.08, 1.20), the absence of systemic manifestations (OR = 0.30, 95% CI 0.08, 1.08), the presence of hypertension (OR = 7.77, 95% CI 0.83, 72.76) and a past history of ischaemic heart disease (OR = 8.65, 95% CI 0.92, 80.95) (Table 2). However, only a statistical trend was observed for these variables.

Continuous data were expressed as mean ± s.d., while categorical variables were expressed as percentages. Comparisons between two categories were made using Student’s two-tailed t-test for continuous variables. To analyse categorical data we performed the chi-square test. When the minimum expected value was <5, Fisher’s exact test was used. Statistical significance was set at P < 0.05.

To identify the best predictors of severe CIEs, multivariate analysis was performed with multiple logistic regression models. Patients were stratified for age as well as for ESR and CRP levels at diagnosis into three groups according to distribution tertiles.

Patients were divided into the following tertiles according to the age at diagnosis: tertile 1 (56–71 yrs); tertile 2 (72–79 yrs); tertile 3 (>80 yrs).

Patients were divided into the following tertiles according to the CRP levels at diagnosis: tertile 1 (<12.03 mg/dl); tertile 2 (12.03–78.10 mg/dl); and tertile 3 (> 78.10 mg/dl). Patients were divided into the following tertiles according to the CRP levels at diagnosis: tertile 1 (0.51–5.37 mg/dl); tertile 2 (5.38–12.02 mg/dl); tertile 3 (> 12.03 mg/dl). However, tertiles 2 and 3 were grouped together because of the low number of patients with cranial manifestations and CRP values at diagnosis.

SPSS software, version 14.0 (SPSS Inc, Chicago, IL, USA) was used for analysis.

Results

Table 1 shows the clinical and demographic characteristics of the 180 patients with biopsy-proven GCA and the comparison of patients with and without severe CIEs. Thirty-three patients experienced visual loss (30 had anterior ischaemic optic neuritis, and 6 had central retinal artery occlusion) and 5 experienced CVAs (vertebro-basilar stroke in all patients). CIEs (visual loss and/or CVAs) occurred in 38 patients.

The age at disease onset was significantly older in patients who did not experience severe CIEs compared with those who did. Systemic signs/symptoms were significantly less frequent and ESR and CRP values at diagnosis were significantly lower in patients with severe CIEs. The prevalence of hypertension and ischaemic heart disease was significantly higher in patients with severe CIEs compared with those without. At the time of diagnosis, 26 of 177 patients (14.7%) had already been receiving long-term treatment with low-dose aspirin (21 patients), ticlopidine (three patients) or anti-coagulant therapy (two patients). Patients treated with long-term anti-platelet/anti-coagulant therapy were significantly more likely to suffer CIEs.

Of the 146 patients who were not taking anti-platelet or anti-coagulant therapy, 141 (97%) had no past history of ischaemic heart disease, while 5 (3%) had a positive history. The frequency of severe CIEs was similar in patients with and without history of ischaemic heart disease (20 vs 18%, respectively).

Of the 25 patients taking anti-platelet or anti-coagulant therapy, 17 (68%) had a negative past history of ischaemic heart disease, while 8 (32%) had a positive history.

The frequency of severe CIEs was significantly higher in the patients with history of ischaemic heart disease compared with those without (75 vs 23.5%, respectively, P = 0.02).
protective. Only few studies have evaluated the influence of ischaemic heart disease, while the presence of systemic manifestations and elevated levels of acute-phase reactants at diagnosis were ischaemic complications. 

In this retrospective cohort study, we showed that major risk factors of severe CIEs were the history of hypertension and ischaemic heart disease, while the presence of systemic manifestations and elevated levels of acute-phase reactants at diagnosis were protective. Only few studies have evaluated the influence of cardiovascular risk factors on the development of severe CIEs in GCA. Gonzalez-Gay et al. [3] found that the presence of at least one of the traditional risk factors studied at the time of GCA diagnosis (hypercholesterolaemia, diabetes mellitus, hypertension or heavy smoking) significantly increased the risk of developing severe CIEs. However, evaluating the factors individually, only hypertension was significantly associated with a higher risk of developing severe CIEs. The same authors in a different study reported in other series [5, 17–19]. Five patients (2.7%) had CVAs in a 19-yr period. In our series, the proportion of patients who developed severe CIEs compared with those without, the difference was not significant. Fever, anorexia and weight loss. The ESR at diagnosis was available for 34 patients with severe ischaemic complications and 156 patients without before starting corticosteroids.

### Table 1. Comparison of patients with and those without severe ischaemic complications

<table>
<thead>
<tr>
<th>Variable</th>
<th>All GCA patients (n=180)</th>
<th>With (n=38)</th>
<th>Without (n=142)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male/female</td>
<td>42/138</td>
<td>12/26</td>
<td>30/112</td>
<td>NS</td>
</tr>
<tr>
<td>Age at onset of disease, mean ± s.d., yrs</td>
<td>74 ± 7</td>
<td>77 ± 5</td>
<td>73 ± 7</td>
<td>0.002</td>
</tr>
<tr>
<td>Jaw claudication</td>
<td>84 (46.7)</td>
<td>47 (44.7)</td>
<td>37 (27.2)</td>
<td>NS</td>
</tr>
<tr>
<td>Systemic signs/symptoms</td>
<td>130 (72.2)</td>
<td>20 (52.6)</td>
<td>110 (77.5)</td>
<td>0.004</td>
</tr>
<tr>
<td>Hypertension risk factors</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypertension</td>
<td>105/161 (65.2)</td>
<td>27/32 (84.4)</td>
<td>78/129 (60.5)</td>
<td>0.01</td>
</tr>
<tr>
<td>Heavy smoking</td>
<td>37/171 (21.6)</td>
<td>7/37 (19.4)</td>
<td>30/134 (22.4)</td>
<td>NS</td>
</tr>
<tr>
<td>Hypercholesterolaemia</td>
<td>23/172 (13.4)</td>
<td>4/38 (10.5)</td>
<td>19/134 (14.2)</td>
<td>NS</td>
</tr>
<tr>
<td>Hypertriglyceridaemia</td>
<td>8/170 (4.7)</td>
<td>1/37 (2.7)</td>
<td>7/133 (5.3)</td>
<td>NS</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>10/173 (5.8)</td>
<td>3/37 (8.1)</td>
<td>7/136 (5.1)</td>
<td>NS</td>
</tr>
<tr>
<td>Cardiac atherosclerosis</td>
<td>56/81 (69.1)</td>
<td>19/24 (75.0)</td>
<td>37/57 (66.7)</td>
<td>NS</td>
</tr>
<tr>
<td>Cerebrovascular accidents</td>
<td>18/172 (10.5)</td>
<td>3/36 (8.3)</td>
<td>15/137 (10.9)</td>
<td>NS</td>
</tr>
<tr>
<td>Ischaemic heart disease</td>
<td>13/173 (7.5)</td>
<td>7/36 (19.4)</td>
<td>6/137 (4.4)</td>
<td>0.006</td>
</tr>
<tr>
<td>Anti-platelet or anti-coagulant therapy</td>
<td>26/177 (14.7)</td>
<td>10/37 (27.0)</td>
<td>16/140 (11.4)</td>
<td>0.03</td>
</tr>
<tr>
<td>ESR, mean ± s.d., mm/1st h</td>
<td>93 ± 28</td>
<td>86 ± 25</td>
<td>96 ± 28</td>
<td>0.03</td>
</tr>
<tr>
<td>CRP, mean ± s.d., mg/dl</td>
<td>9.9 ± 6.2</td>
<td>7.2 ± 4.5</td>
<td>10.4 ± 6.3</td>
<td>0.04</td>
</tr>
</tbody>
</table>

*Except where indicated otherwise, values are the (%) of patients. P-values are for the comparison between GCA patients with severe ischaemic complication symptoms and those without severe ischaemic complications. NS: not significant. Fever, anorexia and weight loss. The ESR at diagnosis was available for 34 patients with severe ischaemic complications and 156 patients without before starting corticosteroids.

### Table 2. Predictive variables of severe ischaemic complications

<table>
<thead>
<tr>
<th>Variable</th>
<th>Z</th>
<th>s.e.</th>
<th>P</th>
<th>OR</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Systemic manifestations</td>
<td>−1.20</td>
<td>0.656</td>
<td>0.066</td>
<td>0.30</td>
<td>0.08</td>
</tr>
<tr>
<td>Coronary artery disease</td>
<td>2.16</td>
<td>1.141</td>
<td>0.059</td>
<td>8.65</td>
<td>0.92</td>
</tr>
<tr>
<td>Hypertension</td>
<td>2.05</td>
<td>1.142</td>
<td>0.073</td>
<td>7.77</td>
<td>0.83</td>
</tr>
<tr>
<td>Elevated CRP, &gt;5.38 mg/dl</td>
<td>−1.18</td>
<td>0.696</td>
<td>0.090</td>
<td>0.307</td>
<td>0.08</td>
</tr>
</tbody>
</table>

In contrast, Nesher et al. [5] in Israel and Lee et al. [7] in Cleveland failed to show an association between cardiovascular risk factors and the development of severe ischaemic complications in GCA. Our findings in Northern Italy are more in agreement with those reported by Gonzalez-Gay et al. [3] in Spain. Of note, hypertension was associated with severe ischaemic complications in both studies.

However, our study is the first evaluating the association of a past history of ischaemic heart disease, stroke or transient attack, as well as of the presence of carotid atherosclerosis with the risk of developing severe CIEs. The presence of underlying atherosclerosis may play a role in the development of these complications.

Atherosclerosis and the GCA inflammatory process may interact increasing the risk of severe CIEs. This hypothesis is supported by recent findings showing that the association of inflammation (elevated CRP levels) with stroke or cardiovascular disease is more apparent in the presence of underlying atherosclerosis [20, 21].

The assessment of atherosclerosis is usually performed by carotid ultrasonography [15, 22]. Therefore, we have reviewed all the scans performed before and after diagnosis for both scanning and interpretation of carotid sonographic images. Furthermore, we have considered only carotid ultrasonography scans performed before GCA clinical manifestations, because after disease onset the interpretation of ultrasonography images may be compounded by the development of arteritic lesions.

Interestingly, similar predisposing risk factors contribute to the risk of developing the arteritic and non-arteritic forms of anterior ischaemic optic neuropathy (AION). Non-arteritic anterior ischaemic optic neuropathy has been found to be associated with arterial hypertension and ischaemic heart disease, but not with carotid atherosclerosis [23, 24].

Two recent studies have demonstrated that anti-platelet/anti-coagulant therapy, started before GCA diagnosis, may reduce the risk of severe CIEs in patients with GCA [7, 25]. However, Gonzalez-Gay et al. [3] did not observe any impact of...
angiogenic activity of IL-6 has been postulated to be an important protective mechanism for ischemia in GCA. Hernández-Rodríguez et al. [26] found that IL-6 expression in temporal artery infiltrates and circulating levels of IL-6 were significantly reduced in patients with ischemic complications. The authors also found that the angiogenic response was lower in GCA patients with ischemic events and in those with weak systemic inflammatory response [27]. These observations may in part explain why patients with a reduced acute-phase response characterized by lower IL-6 production are at higher risk of developing severe CIEs.

Limitations of our study include its retrospective cohort design and the inherent impossibility to ascertain traditional cardiovascular risk factors and carotid atherosclerosis at regular intervals. Single determinations of cholesterol, triglycerides or glucose levels, and single ultrasonographic evaluation of carotid atherosclerosis may neither accurately represent average concentrations and atherosclerotic disease course over time nor cumulative burden of exposure. Furthermore, although all specialized medical care for the Reggio Emilia area is provided at the Santa Maria Nuova Hospital, it is possible that some historical data may have escaped the recording system. Ascertainment bias may therefore affect our results. However, our study also has several strengths. This group includes a population-based design, the use of temporal artery biopsy for identifying GCA patients, and the application of rigorous and validated criteria to define cardiovascular risk factors and carotid atherosclerosis.

In conclusion, the history of ischemic heart disease and hypertension, together with the presence of a lower inflammatory state, appear to contribute to the development of severe CIEs in GCA. Physicians who care for GCA patients should be aware of the higher risk of CIEs in patients with these cardiovascular and inflammatory statuses at diagnosis. The knowledge of these risk factors can aid to identify high-risk patients that may benefit from aggressive treatment.

**Rheumatology key messages**

- Hypertension, previous ischemic heart disease and low inflammation are associated with a higher risk of developing ischemic events in GCA.
- Anti-platelet or anti-coagulation therapy did not reduce the risk of cranial ischemic events in GCA.

**Disclosure statement:** The authors have declared no conflicts of interest.

**References**