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**Cerebrovascular events are associated with lower survival in giant cell arteritis: a case-  
controlled multicenter study**

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Giant-cell arteritis (**GCA**) is a large-vessel vasculitis usually affecting individuals over 50 years old; half of cases are associated with polymyalgia rheumatica [1]. The aorta and its large arterial branches are typically involved, particularly the branches of the external carotids, leading to headache, jaw claudication, scalp tenderness and temporal artery thickening [2]. GCA affects the aorta and its large branches in up to 83% of cases, leading to aneurysms or arterial stenosis [3]. Internal carotids and vertebral arteries are less commonly involved and may be responsible for ischemic cerebrovascular events in cases of stenosis or occlusion. Strokes in GCA patients occur frequently in the first year after diagnosis and may sometimes be the initial symptom of GCA. The impact of stroke on mortality in GCA patients has not been well evaluated.

Thus, we conducted a retrospective, multicenter, case-controlled study to evaluate the survival of patients with cerebrovascular events in GCA and to characterize the clinical and imaging presentations of this GCA manifestation, in the department of internal medicine and the stroke unit of a French university hospital. Patients who received a definite diagnosis of GCA according to the American College of Rheumatology criteria [2, 4] and who experienced a cerebrovascular event were identified through the computerized local database (Programme de Médicalisation des Systèmes d'Information, PMSI). Cerebrovascular events related to atrial fibrillation or overt atherosclerotic lesions were excluded. The control group patients were also identified through the PMSI and medical records were obtained to confirm the absence of neurological signs. These patients had also received a definite GCA diagnosis and were matched in a 1:1 ratio on sex and age at GCA diagnosis with patients of the group "cerebrovascular event". Differences between groups were tested using the Mann-Whitney U test for continuous data and Fisher's exact test for qualitative data. Survival curves were built with the Kaplan-Meier method, considering the time of

diagnosis of GCA to death or last follow-up. All tests were two-sided and a p-value < 0.05 was considered statistically significant. Statistical analyses were performed using GraphPad Prism V 6.0 (GraphPad software, La Jolla, CA, USA).

Fourteen patients receiving a diagnosis of GCA between 2002 and 2016 and having a cerebrovascular accident at diagnosis or during follow-up were included as well as 14 controls matched on sex and age at GCA diagnosis. Baseline characteristics of the patients are detailed in **Table 1**.

The characteristics of the cerebrovascular events are detailed in **Table 2**.

Four patients died during follow-up in the cerebrovascular event group and one in the control group. The survival was greater in the control group (p=0.03, **Figure 1**). Two patients died shortly after stroke because of recurrence of ischemic events in one patient and hemorrhagic transformation for the other. The cause of death for the 2 other patients was not known.

The stroke relapsed in 2 patients (14 %) after 10 days and 58 months, respectively. Two patients experienced post-stroke seizures during the follow-up and were treated with an anti-epileptic drug. At the end of the follow-up, 5 patients out of 10 (50 %) had persistent neurologic sequelae.

In this study, we demonstrate that the mortality is higher in GCA patients with cerebrovascular events. The occurrence of stroke among GCA patients has been described in several series or isolated case reports [5-15]. A recent meta-analysis confirmed the increased risk of cerebrovascular events among this population (risk ratio of 1.4 with 95% CI: 1.27-1.56) [15]. In our study, 4 patients had a stroke as the initial sign of GCA. Three additional patients had a stroke a few days after the diagnosis of GCA and the initiation of corticosteroids. This finding was consistent with studies showing that the risk of cerebrovascular events was higher during the first year after GCA diagnosis or even during the first month [6, 14]. We found that strokes occurring during GCA more likely involved the vertebrobasilar territory, accounting for 35 % of events,

whereas it usually represents less than 15% in atherosclerotic or cardioembolic cerebrovascular events [16]. There was no difference in our study between cases and controls in the frequencies of cardiovascular risk factors despite previous studies that reported that strokes in GCA were associated with more cardiovascular risk factors [17], which suggested that intracranial vessel involvement is a specific manifestation of the disease. The temporal link between GCA flares and strokes is highly suggestive of an inflammatory mechanism for stroke in GCA patients rather than an atherosclerotic mechanism. Finally, we demonstrated that GCA patients with stroke have a lower survival than sex- and age-matched GCA patients who do not have clinical signs of cerebrovascular involvement. Some studies report that low dose aspirin use may decrease the risk of cerebrovascular events during GCA follow-up while others could not find a significant benefit of antiplatelet therapy or statin use in preventing these events [10, 18]. Given the mortality and neurologic sequelae associated with stroke in GCA, the use of an immunosuppressive drug in addition to standard corticosteroids should be considered in case of inflammatory vascular disease.

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TC, PC, CR, BH, PR and FCA contributed to the acquisition of data.

TC and FCA conducted the statistical analysis.

ZA and FCA coordinated the study.

All the authors approved the final submitted version.

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Figure 1. Survival in GCA patients with and without stroke showing significant lower survival in patients with stroke (p=0.03).

	<b>GCA patients with stroke (N = 14)</b>	<b>Controls (N = 14)</b>
<b>Age (at GCA diagnosis), years, median (range)</b>	73.5 (65-82)	73.5 (65-83)
<b>Male/Female</b>	3/11	3/11
<b>Follow-up duration, years, median (range)</b>	5.26 (0.1-12.3)	3.81 (0.55-7.16)
<b>Cardiovascular disease risk factors</b>		
- Smoking, pack-years	21.4 (26.8)	6.86 (10.7)
- Dyslipidemia (%)	6 (42%)	4 (28%)
- Hypertension (%)	10 (71%)	8 (57%)
- Diabetes mellitus (%)	3 (21%)	4 (28%)
- Coronaropathy (%)	3 (21%)	2 (14%)
- Body mass index, median (range)	24.85 (19.5-33)	24.08 (16.4-51)
- Familial history of MI or stroke (%)	1 (7%)	0 (0%)
- Peripheral artery disease (%)	2 (14%)	1 (7%)
<b>Atrial fibrillation (%)</b>	0 (0%)	0 (0%)
<b>Symptoms at diagnosis</b>		
- Headaches (%)	10 (71%)	10 (71%)
- Vision impairment (%)	6 (42%)	4 (28%)
- Scalp tenderness (%)	7 (50%)	7 (50%)
- Jaw claudication (%)	5 (35%)	7 (50%)
- Fever (%)	4 (28%)	8 (57%)
- Loss of weight (kg), mean (SD)	-1.9 (2.90)	-2.5 (2.98)
- Arthralgia (%)	7 (50%)	8 (57%)
<b>Biological tests at GCA diagnosis (median)</b>		
- ESR (mm/h)	76 (33)	79 (41)
- CRP (mg/L)*	49.5 (50.1)	122 (121)
- Fibrinogen (g/L)	6.96 (2.5)	8.08 (2.3)
- Hb (g/dL)	11.9 (1.12)	11.4 (1.95)
- Platelets (x 10 <sup>3</sup> /mm <sup>3</sup> )	453 (189)	414 (150)
<b>Positive temporal artery biopsy (%)</b>	11 (78%)	7 (50%)
<b>Treatment at diagnosis</b>		
- Corticosteroids (%)	14 (100%)	14 (100%)
- Methotrexate (%)	2 (14%)	0 (0%)
- Antiplatelet therapies (%)	11 (78%)	9 (64%)
<b>Death (%)</b>	4 (28%)	1 (7%)

**Table 1. Demographic, clinical and biological presentation of cases and controls.**

GCA: giant-cell arteritis, MI: myocardial infarction, SD: standard deviation, GGT: gamma glutamyl transferase, Hb: hemoglobin, ESR: erythrocyte sedimentation rate; CRP: C-reactive protein \* p < 0.05



Stroke features	GCA patients with stroke N = 14
<b>Symptoms</b>	
- Headache (%)	5 (35%)
- Aphasia (%)	2 (14%)
- Hemiparesis (%)	10 (71%)
- Cerebellar ataxia (%)	1 (7%)
- Visual impairment (%)	3 (21%)
<b>Transient ischemic attack (%)</b>	1 (7%)
<b>Ischemic stroke (%)</b>	13 (93%)
<b>Median NIHSS at admission (range)</b>	3 (0-17)
<b>Involved territory</b>	
- Anterior cerebral artery (%)	0 (0%)
- Middle cerebral artery (%)	8 (57%)
- Posterior cerebral artery (%)	5 (35%)
- Cerebellar artery (%)	1 (7%)
<b>Multiple infarcts (%)</b>	6 (42%)
<b>Internal carotid stenosis (%)</b>	6 (42%)
<b>Internal carotid thrombosis (%)</b>	1 (7%)
<b>Vertebral artery stenosis (%)</b>	7 (50%)
<b>Vertebral artery thrombosis (%)</b>	0 (0%)
<b>Basilar artery stenosis (%)</b>	3 (21%)
<b>CRP at time of stroke (mg/L), median (range)</b>	6 (2-68)
<b>Treatment at stroke diagnosis</b>	
- Corticosteroids (%)	6 (42%)
- Corticosteroids, median dose (mg/day) (SD)	14 (25)
- Statin (%)	4 (28%)
- Antiplatelet therapy (%)	4 (28%)
- Immunosuppressive drug (%)	0 (0%)
<b>Treatment after stroke</b>	
- Thrombolytic therapy (%)	1 (7%)
- Antiplatelet therapy (%)	11 (78%)
- Anticoagulants (%)	4 (28%)
- Corticosteroids (%)	11 (78%)
Median dose (mg/day), (range)	60 (10-70)
- Intravenous methylprednisolone	3 (21%)
- Methotrexate (%)	2 (14%)
- Tocilizumab	0 (0%)
<b>Outcomes</b>	
- Neurologic sequelae at the end of follow-up (%)	5 (35%)
- Stroke recurrence	2 (14%)
- Epilepsy	2 (14%)
- Cognitive impairment	1 (7%)
- Mortality at 2 months	2 (14%)

**Table 2. Characteristics of stroke in GCA patients.** NIHSS: National Institute of Health Stroke Scale; CRP C-reactive protein

