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Ischemic stroke in giant-cell arteritis: French retrospective study

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ABSTRACT

Acute cerebrovascular ischemic events are a rare and severe complication of giant cell arteritis (GCA). We aimed to determine the prevalence of GCA-related stroke, the overall survival and the relapse-free survival in patients with GCA.

A multicentric retrospective analysis was performed on 129 patients with GCA diagnosed between September 2010 and October 2018 in two University Hospitals. Among 129 GCA patients, 18 (16%) presented an acute ischemic cerebrovascular event. Patients with stroke were older (83 [67–96] years versus 76 [58–96]; p = 0.014) and more frequently males (61% versus 30%; p = 0.014) than those without stroke. The frequency of anterior ischemic optic neuropathy was higher in patients with stroke (n = 6, 33%) than patients without stroke (n = 12, 11%)(p = 0.02). Overall survival was significantly decreased in GCA patients with stroke (4.4 months), comparatively to patients without stroke (221.7 months; log rank test = 0.006). The 3-years relapse-free survival was decreased in patients with stroke (8.42 versus78.0 months; log rank = 0.0001), as well as the time with sustained remission (78 versus 139 months; log rank test = 0.0004). This study shows the prevalence and risk factors of ischemic stroke in GCA.

1. Introduction

Giant cell arteritis (GCA) is a granulomatous arteritis affecting the aorta and its main branches, particularly carotid arteries [1]. Internal carotid and vertebrobasilar artery involvement is rare and can result in cerebrovascular ischemic events due to arterial stenosis or thrombosis. The occurrence of stroke is a rare complication of GCA, with a prevalence of 2–7% [2–10]. GCA-related strokes can sometimes be difficult to distinguish from strokes of atherosclerotic origin. It is notably difficult in elderly patients who accumulate cardiovascular risk factors and are treated with high-dose steroids. A recent study showed that patients with GCA-related strokes had a reduced survival rate, when excluding strokes of atherosclerotic and embolic origins [7]. Data about the risk of relapse, as well as remission duration are still lacking in this population.

In this study, we aimed to determine the prevalence of stroke in GCA patients and the factors associated with their occurrence, as well as the overall and relapse-free survival of GCA patients with stroke.

2. Patients and methods

2.1. Patients

We consecutively selected for this retrospective study all GCA patients diagnosed between September 2010 and October 2018, in 2 university hospitals (Saint Antoine and Tenon Hospitals). Patients were included in the GCA-related stroke group if they had: (1) a diagnosis of GCA with the fulfillment of at least three criteria according to the American College of Rheumatology (ACR); (2) the occurrence of a transitory or constituted ischemic cerebrovascular event; (3) a delay between GCA diagnosis and stroke inferior to 12 months; (4) no other etiology of stroke, notably the absence of atrial fibrillation at the time of stroke.

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Data regarding age, gender, time from the GCA diagnosis, clinical manifestations, computed tomography angiography data, acute-phase reactants (erythrocyte sedimentation rate and C-reactive protein levels), treatments and outcome were retrospectively collected at the time of GCA diagnosis, stroke and last visit. Sustained remission was defined as clinical and biological remission with steroids less than 10 mg/day for at least 3 months.

2.2. Statistical analysis

Data are expressed as medians with ranges for continuous variables and frequencies with percentages for qualitative variables. Non-parametric Mann-Whitney test and Fisher exact tests were used as appropriate to determine the difference between the groups. Survival curves and time to relapse were expressed with Kaplan Meier curves and tested with log rank test. Multivariable adjusted analyses were not performed, due to the low amount of GCA patients with stroke. Statistical analyses were carried out using GraphPad Prism version 5.1 (GraphPad Software, San Diego, 2007). A p value < 0.05 was considered as statistically significant.

3. Results

3.1. Patients' characteristics

3.1.1. Patients' characteristics at GCA diagnosis

One hundred twenty-nine patients with GCA were included with a median age of 77 years [58–96], 85 (66%) women, and fulfilled median 4 ACR criteria [3–5] (Table 1). Temporal artery biopsy was positive in 80 (62%) patients. Steroids were used in all patients at diagnosis with median of 45 mg/day [25–90], preceded by intravenous pulses in 11 (8%) cases. Steroid-dependence was noted in 27 (21%) patients during the follow-up. Cardiovascular risk factors were present in 88 (64%) patients, including arterial hypertension (n = 49, 38%), tobacco use (n = 40, 31%), diabetes (n = 20, 16%) and hyperlipidemia (n = 24, 19%).

Table 1
GCA patient's characteristics with and without stroke.

Characteristics at diagnosis	All GCA (n = 129)	GCA without Stroke (n = 111)	GCA with stroke (n = 18)
Age (years)(median; ranges)	77 [58–96]	76 [58–96]	83 [67–96]*
Male sex (n; %)	44 (34)	33 (30)	11 (61)*
Headaches (n; %)	89 (69)	74 (67)	15 (83)
Temporal induration/Jaw claudication (n; %)	43 (33)	35 (32)	8 (44)
Fever/Weight loss (n; %)	43 (33)/39 (30)	37 (33)/31 (28)	6 (33)/8 (44)
AION (n; %)	18 (14)	12 (11)	6 (33)*
PMR (n; %)	23 (18)	19 (17.12)	4 (22)
Aortitis (n; %)	10 (8)	7 (6.31)	3 (17)
Positive TAB (n; %)	80 (62)	66 (59)	14 (78)
C-reactive protein (mg/L) (median; ranges)	63 [10–350]	62 [12–350]	66 [10–211]
Cardiovascular risk factors			
Diabetes mellitus (n; %)	20 (16)	15 (14)	5 (28)*
Arterial hypertension (n; %)	49 (38)	39 (35)	10 (56)
Smokers (n; %)	40 (31)	33 (30)	7 (39)
Hyperlipidemia (n; %)	24 (19)	19 (17)	5 (28)
Treatment at GCA diagnosiss			
Steroids (mg/day) (medians; ranges)	45 [10–90]	40 [10–80]	60 [35–90]
All Immunosuppressive therapy	15 (12)	15 (14)	0
- Methotrexate (n; %)	11 (9)	11 (10)	0
- Tocilizumab (n; %)	4 (3)	4 (4)	0
Aspirin (n; %)/Statins (n; %)	31 (24)/21 (16)	22 (20)/16 (15)	9 (50)/5 (28)
Steroid dependence (n; %)	27 (21)	25 (23)	2 (11)
Follow-up (years)(medians; ranges)	2.8 [0.1–24]	3 [0.16–24]	1.3 [0.08–4]*

*$p < 0.05$.
Values are medians with ranges and numbers with frequencies.
GCA: giant cell arteritis; TAB: temporal artery biopsy; AION: anterior ischemic optic neuropathy; PMR: polymyalgia rheumatica.

3.1.2. Cerebrovascular ischemic events

Among GCA patients, 18 (16%) presented a transitory ischemic event or constituted stroke. The median time after GCA diagnosis was 1.6 months [0–9.6]. An ischemic event occurred concomitantly to the diagnosis of GCA in 7 cases and in the year following the GCA diagnosis in 11 cases.

At the time of the ischemic event, GCA symptoms were headaches in 16 (89%) patients, signs of polymyalgia rheumatica (n = 3) and acute anterior neuropathy (n = 1). Acute-phase reactants were increased in 15 cases (83%) at the time of stroke occurrence. Four (22%) patients were treated by aspirin when stroke occurred. The neurological symptoms during stroke were focal motor or sensory deficits (n = 3; 17%), aphasia (n = 3; 17%), impaired consciousness (n = 3; 17%), cranial nerve impairment (n = 2; 12%), cerebellar syndrome (n = 9; 50%), vestibular syndrome (n = 6; 33%). Magnetic resonance brain imaging revealed ischemic lesions which were situated in the vertebrobasilar (n = 11) and carotid territories (n = 5) (Table 1). Stenosis and/or vascular occlusion were observed in vertebral arteries in 11 patients, with a bilateral involvement in 6 cases; basilar artery in 2 cases, circle of Willis in 2 cases, and internal carotid in 1 patient. Fluorodeoxyglucose-positron emission tomography (FDG-PET) imaging was available at the time of the ischemic event in 9 patients and was abnormal in 5 patients, with a FDG uptake of vertebral arteries in 5 cases, internal carotid in 2 cases and diffuse aortitis in 1 case.

Among the strokes occurring after diagnosis of GCA, there were no factors which were predictive of stroke occurrence among: GCA characteristics, steroid dose, steroid dependence, aspirin and statin use.

When comparing GCA patients with and without an ischemic event, GCA patients with stroke were significantly older (median age 83 [67–96] years vs 76 [58–96]; p = 0.014) and more frequently males (61% vs 30%; p = 0.014). The frequency of anterior ischemic optic neuropathy was more important in GCA patients with stroke (6 (33%) vs 12 (11%); p = 0.02). There were no other significant differences in clinical features, frequency of positive temporal biopsy, C-reactive protein levels between GCA patients with and without stroke at the time of GCA diagnosis. Importantly, among cardiovascular risk factors, only the presence of diabetes mellitus was significantly more frequent in patients which experienced stroke during the follow-up (6 (28%), versus 15 (14%), p = 0.02). Median daily amounts of steroids were significantly more important in patients with GCA-associated stroke (60 [35–90] mg/day versus 40 [10–80] mg/day; p = 0.0012). The relapse rate, steroid dependence and number of deaths were not significantly different in patients with and without stroke (data not shown).

3.1.3. Outcome after stroke

Ten patients (56%) with ischemic stroke received intravenous steroids pulses (250 mg–1000 mg, 3 days) followed by 60 mg/day [40–90] oral prednisone. NIHSS scale decreased from baseline 1 [0–7] to 0 [0–4] at 3, 6 and 12 months respectively (p = 0.06) (Supplemental Table 2). Rankin scales were not significantly different from 1 [0–4] at baseline to 1 [0–3] at 3 months, 0 [0–3] and 0.5 [0–3] at 6 and 12 months, respectively (p = 0.6). C-reactive protein levels significantly decreased from 35 [5–211] mg/l at baseline to 1 [0–30] at 3 months and 1 [0–5] and 1 [0–1] at 6 and 12 months, respectively ($p < 0.0001$). Steroids dose significantly decreased from 60 [40–90] mg at the time of stroke to 10 [5–0] mg at 6 months and 5 [0–20] mg at 12 months ($p < 0.0001$).

The overall survival was significantly decreased in GCA patients with stroke, with 10th survival percentile of 4.4 months versus 221.7 months in GCA without stroke (log rank test = 0.006) (Fig. 1). The 3-

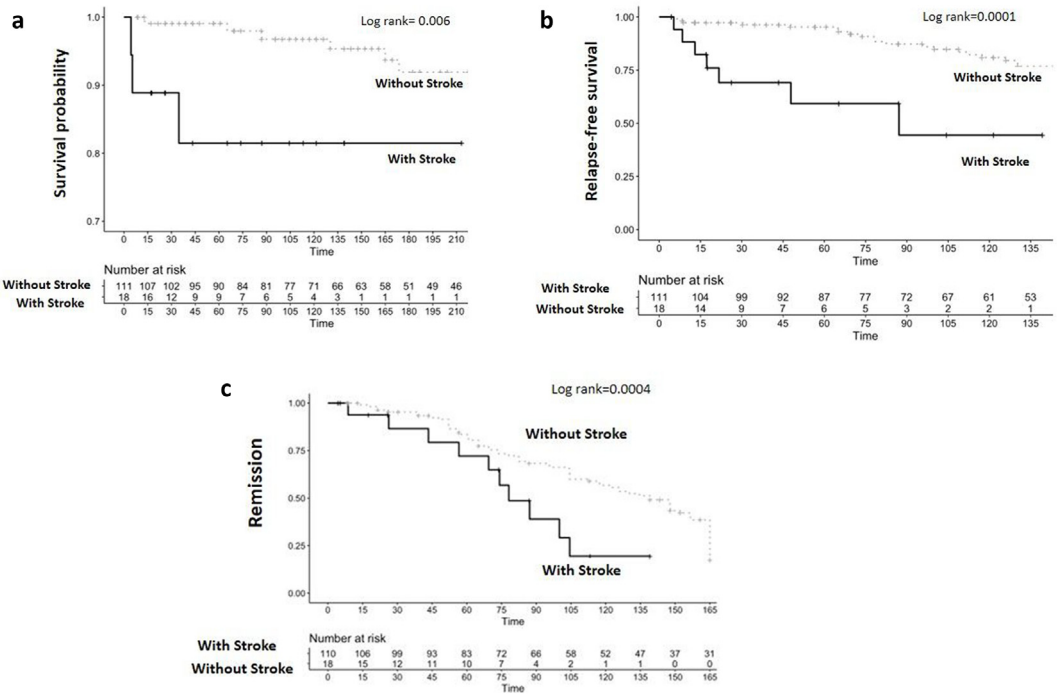

Fig. 1. A Overall survival of GCA patients with and without stroke; BRelapse-free survival in patients with and without stroke; C Time of remission in GCA patients with and without stroke.

years relapse-free survival was significantly decreased in GCA patients with stroke with 10th survival percentile of 8.42 months versus 78.0 months (log rank test = 0.0001) (Fig. 1b). The time with sustained remission was also significantly decreased in GCA patients with stroke (median at 78 versus 139 months; log rank test = 0.0004) (Fig. 1c).

4. Discussion

Cerebrovascular ischemic events was noted in 16% of GCA patients. These patients were older males, presented more often anterior ischemic optic neuropathy and with a more frequent past of diabetes. Occurrence of stroke significantly impaired the overall survival, the relapse free survival and the time of sustained remission in comparison with patients without stroke.

The prevalence of ischemic stroke in GCA varies from 2 to 20% according to various studies [10–12]. In this study we selected GCA strokes occurring in the year after the diagnosis, as GCA could still be active, and patients under steroids. Previous large studies noted a hazard ratio of stroke in patients with GCA of 2.04 [95% CI 1.43; 2.93] and increased to 3.20 [95% CI 1.43; 2.93] in the first year following the diagnosis of GCA [13]. The difference between GCA-related strokes and cardiovascular-related strokes could not be distinguished in these studies. In our study, more than 80% of patient had GCA symptoms and high levels of acute phase reactants at the time of stroke.

The risk factors of developing an ischemic stroke in GCA patients were mainly male sex, older age, previous diabetes and associated anterior ischemic optic neuropathy. Previous studies showed various risk factors, such as male sex, smoking, high blood pressure, polycythemia, and vision loss; whereas other studies found no risk factors [3,6,14]. The prevalence of stroke due to the involvement of vertebrobasilar arteries could be estimated at 40–60% of strokes in GCA, in contrast with atherosclerosis where only 15–20% of strokes are localized in this area [15]. Distinguishing GCA vasculitis involvement from atherosclerotic lesions could sometimes be difficult. Indeed, vascular imaging can fail to show artery thickening or stenosis, and the prevalence of atherosclerotic lesions is frequent in elderly patients with cardiovascular risk factors [16]. No pathognomonic signs in cerebral imaging allow to assert stroke origin, but the presence of stenosis or occlusions in supra-aortic vessel segments, and in some rare cases an arterial “halo” on the carotid or vertebral arteries could be suggestive of vasculitis [17,18]. Several limitations could be acknowledged, as the study is retrospective and had a low amount of patients with stroke. Only prospective studies could finally ascertain the prevalence and risk factors of stroke in GCA patients.

5. Conclusion

This study shows a high prevalence of ischemic stroke in GCA patients, who were mainly males, older, and presenting an anterior ischemic optic neuropathy. The place of immunomodulation strategies combined to steroids in the treatment of GCA-related strokes need to be evaluated in prospective studies.

Conflicts of interest and funding

None.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jaut.2019.01.009.

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