Giant Cell Arteritis–related Stroke: A Retrospective Multicenter Case-control Study

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ABSTRACT. ***Objective.*** Our aim was to describe patients with giant cell arteritis (GCA)–related stroke and to compare them with a control group of GCA patients without stroke.

Methods. We created a retrospective multicenter cohort of patients with (1) GCA diagnosed according to the American College of Rheumatology criteria between 1995 and 2015, and (2) stroke occurring at the time of GCA diagnosis or occurring within 4 weeks of starting GCA therapy. The control group consisted of GCA patients without stroke.

Results. Forty patients [21 women (53%), median age 78 (60–91) yrs] with GCA-related stroke were included and were compared with 200 control patients. Stroke occurred at GCA diagnosis in 29 patients (73%), whereas it occurred after diagnosis in 11 patients. Vertebrobasilar territory was involved in 29 patients (73%). Seven patients died within a few hours or days following stroke. Compared with the control group, stroke patients had more ophthalmic ischemic symptoms [25 (63%) vs 50 (25%), $p < 0.001$]. Conversely, they demonstrated lower biological inflammatory variables [C-reactive protein: 61 (28–185) mg/l vs 99 (6–400) mg/l, $p = 0.04$] and less anemia [22/37 (59%) vs 137/167 (79%), $p = 0.03$] than patients without stroke. Multivariate logistic regression revealed that the best predictors for the occurrence of stroke were the presence of ophthalmic ischemic symptoms at diagnosis (OR 5, 95% CI 2.14–12.33, $p = 0.0002$) and the absence of anemia (OR 0.39, 95% CI 0.16–0.99, $p = 0.04$).

Conclusion. Stroke, especially in the vertebrobasilar territory, is more likely to occur in patients with GCA who experience recent ophthalmic ischemic symptoms and who exhibit low inflammatory variables. (J Rheumatol First Release January 15 2017; doi:10.3899/jrheum.161033)

Key Indexing Terms:
CEREBROVASCULAR DISORDERS GIANT CELL ARTERITIS
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Giant cell arteritis (GCA) is the most common form of systemic vasculitis in patients over 50 years of age. The inflammatory process leads to vessel scarring, narrowing, severe stenosis, and eventually occlusion. The involvement of large vessels, especially the carotid branches, explains the predominantly cranial symptoms such as headache, scalp tenderness, temporal artery stiffness, and jaw claudication. Involvement of ophthalmologic vessels (ophthalmic artery and/or posterior ciliary arteries) is frequent and may be responsible for permanent or transient visual loss, especially because of acute optic nerve ischemia. Cerebrovascular accidents (CVA) have been described in the GCA context and may occur at disease onset in 2.8% to 7.2% of patients[1,2,3,4,5,6,7]. In contrast to the usually well-recognized cranial and ophthalmic signs of GCA caused by the ischemic tissue being drained by the external carotid and internal

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carotid arteries, respectively, GCA-related stroke may be more widely attributed to vertebrobasilar artery involvement[1,2,3,4,5,6,7]. Because stroke is a leading cause of morbidity and mortality in GCA, more extensive knowledge of this rare complication is required. Thus, we created a cohort of patients with GCA-related stroke and compared it with a control group of GCA patients without stroke. We set out to describe their presentation at diagnosis and to identify predictive factors of stroke.

MATERIALS AND METHODS

Study design and patients. Patients were retrospectively selected through an e-mail sent to physicians belonging to 4 GCA referral centers [Caen, Limoges, Dijon, and Bichat (Paris, APHP) University Hospital]. Using a computerized database, patients diagnosed with GCA and stroke were listed and reported to the study investigator.

To be eligible for inclusion, patients had to fulfill the following 2 criteria: (1) diagnosis of GCA between 1995 and 2015 according to the American College of Rheumatology (ACR) criteria[8], and (2) ischemic stroke occurring at the time of diagnosis of vasculitis or within 4 weeks of starting GCA therapy. We did not include (1) patients with isolated ophthalmic ischemic symptoms, which can be confused with symptoms specific to GCA, (2) patients with a transitory cerebrovascular ischemic event, (3) patients with a stroke that occurred before the working diagnosis of GCA or in the absence of signs suggesting GCA, including new onset of cranial symptoms or signs of polymyalgia rheumatica (PMR) or absence of a significant increase in laboratory inflammatory variables, and (4) patients with a stroke that occurred more than 4 weeks after treatment initiation, given that the inflammatory condition would most likely be under control by that time.

Patients with new-onset atrial fibrillation at the time of stroke were excluded. Patients with longterm atrial fibrillation and a normal echocardiogram along with efficient anticoagulation on several consecutive laboratory tests were included.

The control group consisted of patients with GCA with no history of stroke from reporting patient centers. For each patient included with stroke, 5 consecutive patients without stroke were included in the control group. All the patients met the ACR criteria. The characteristics of GCA presentation, temporal artery biopsy (TAB) status, and laboratory test results for all included and control group patients were collected.

We conducted our study in accordance with good clinical practice guidelines and the Declaration of Helsinki. Caen University Hospital Ethics Committee approved the study (CPP Nord Ouest 3 – Hortostroke). The manuscript was prepared in accordance with the Strengthening The Reporting of OBservational studies in Epidemiology guidelines.

Study variables and definitions. A standardized data collection form was sent to reporting physicians. At GCA diagnosis, demographic data, medical history including cardiovascular (CV) events and risk factors [tobacco consumption, hypertension (HTN), hypercholesterolemia, diabetes mellitus], clinical symptoms related to GCA, laboratory variables [including hemogram (anemia was defined as a hemoglobin level of < 13 g/dl in men and < 12 g/dl in women), ionogram, erythrocyte sedimentation rate (ESR), and C-reactive protein (CRP)] were collected in both groups. At the time of stroke, symptoms related to stroke (including vascular and cardiac murmurs, vascular pulses, and arterial tension monitoring), the time between GCA diagnosis and neurological symptoms, and the results of brain imaging were noted. When available, vascular brain imaging was analyzed. All enrolled patients were checked for cardioembolic disease (electrocardiogram, echocardiogram). Treatment, outcomes, and followup time were collected in patients with GCA-related stroke.

A relapse was defined as the reoccurrence of clinical symptoms and/or increase in inflammatory variables not attributable to a condition other than GCA.

As we set out to describe patients with GCA-related stroke and identify some differences in disease presentation between patients with GCA-related stroke and controls, data on disease course and outcomes (relapse, death, management of treatment) were not collected from control patients.

GCA-related stroke incidence in each center was estimated based on the number of strokes occurring in patients followed up for GCA over a set period. The computerized database in each center was used to assess the number of patients with GCA who were followed up.

Statistical analyses. Categorical variables are expressed as a number (%) and quantitative variables as median (range). Categorical variables were analyzed using the chi-square test or Fisher's exact test, as appropriate, and the quantitative variables using Wilcoxon rank-sum test. Multivariate logistic regression analysis was performed to determine factors independently associated with stroke using variables that reached $p < 0.2$ on univariate analysis. The results were adjusted for CV risk factors (age, smoking, HTN, diabetes, and hypercholesterolemia).

Statistical analyses were computed with JMP 9.0.1. A p value of ≤ 0.05 defined statistical significance.

RESULTS

Patients' characteristics at diagnosis. Forty-nine patients were reported, but 9 did not meet all of the inclusion criteria and were excluded from the study: 4 patients experienced a stroke that was more likely to be related to a cardiac thromboembolic event (new-onset atrial fibrillation) rather than GCA diagnosed 2, 5, 12, and 17 months earlier, respectively, and in clinical and biological remission with glucocorticoids (GC) at the time of the neurovascular event; 4 other patients had a stroke before GCA was diagnosed (6, 7, 15, and 22 mos, respectively); and 1 patient had met only 2 ACR criteria.

Overall, 40 patients [21 women (53%), median age 78 (60–91) yrs] were analyzed. The detailed characteristics are shown in Table 1.

Apart from age, 18 patients (44%) had ≥ 2 standard CV risk factors, including ischemic heart disease. GCA diagnosis was established on ≥ 3 ACR criteria [median 4 (3–5)] in all patients and TAB was positive in 33 (83%). There were 200 patients with GCA enrolled in the control group. Their characteristics are shown in Table 1.

All patients had increased inflammatory variables except 4 with CRP levels at < 15 mg/l (normal < 5 mg/l), but with a positive TAB.

Considering the usual risk factors for stroke (Table 1), no significant difference was observed between patients with GCA-related stroke compared with the control group, except for age: median age of 78 years (60–91) for stroke patients versus 74 years (50–94) for the controls ($p = 0.03$).

Cerebrovascular events. Stroke occurred at GCA diagnosis in 29 patients (73%), whereas it occurred post-diagnosis in 11 patients, 6 (1–14) days after the initiation of GC. The neurological symptoms at the time of stroke are given in Table 2.

At the time of stroke (and on previous laboratory tests), 2 patients (5%) had longterm atrial fibrillation with efficient anticoagulation and a normal echocardiography (no intracardiac thrombus).

No differences were observed between patients whose stroke occurred at GCA diagnosis and those who experienced

Table 1. Characteristics of 40 patients with GCA-related stroke and 200 control patients. Values are n (%) or median (range) unless otherwise specified.

Characteristics	Patients with Stroke, n = 40	Control, n = 200	p
Demographics			
Female/male, n	21/19	127/73	0.19
Age, yrs	78 (60–91)	74 (50–94)	0.03
CV risk factors			
Current smoker	13 (33)	42/188 (22)	0.17
Diabetes mellitus	8 (20)	26/198 (13)	0.26
Hypercholesterolemia	12 (30)	51/198 (26)	0.58
Hypertension	27 (68)	115/198 (58)	0.27
Coronary disease	6 (15)	22/198 (11)	0.49
≥ 2 CV risk factors	18 (44)	71 (36)	0.26
Anti-aggregation before GCA diagnosis	13 (33)	72 (36)	0.67
GCA characteristics			
Fever	10 (25)	53 (27)	0.44
Headaches	29 (73)	161 (81)	0.29
Abnormal temporal artery on physical examination	21 (53)	62/140 (44)	0.36
Scalp tenderness	16 (40)	65/143 (45)	0.54
Jaw claudication	14 (35)	60/146 (41)	0.49
Ophthalmic ischemic symptoms	25 (63)	50 (25)	< 0.001
Polymyalgia rheumatica	8 (20)	76/198 (38)	0.03
Erythrocyte sedimentation rate, mm*	68 (10–119)	80 (10–140)	0.003
C-reactive protein, mg/l	61 (28–185)	99 (6–400)	0.04
Fibrinogen, g/l	6 (4.5–9.77)	6.70 (3.70–11.46)	0.23
Hemoglobin, g/dl	12 (9.4–16.1)	11.1 (7.8–15.8)	0.02
Anemia	22/37 (59)	137/167 (79)	0.03
Platelets, g/mm^3	383 (99–957)	396 (126–913)	0.69
Positive temporal artery biopsy	33 (83)	134 (67)	0.17

* Data available in 228 patients. GCA: giant cell arteritis; CV: cardiovascular.

Table 2. Characteristics of neurological manifestations in giant cell arteritis–related stroke. Values are n (%).

Characteristics	Values
Focal motor or sensory deficit	17 (41)
Aphasia	10 (24)
Facial palsy	13 (32)
Impaired vigilance	8 (20)
Acute cognitive disorder	6 (15)
Cranial nerve involvement	7 (17)
Cerebellar syndrome	14 (34)
Vestibular syndrome	6 (15)

a stroke following GCA diagnosis (regarding demographics, clinical manifestations, laboratory variables, TAB status).

All patients except 2 underwent brain imaging at the time of the neurologic event. Two patients did not undergo brain imaging because their clinical condition did not permit it. Both patients had biopsy-proven GCA and had initiated GC 1 day and 9 days before the stroke, respectively, with no associated anticoagulant treatment. They showed acute impaired vigilance along with cranial nerve involvement and sudden death suggesting brainstem stroke.

Brain imaging revealed ischemic lesions in the other 38 patients. Fourteen patients underwent a computed tomography (CT) scan, which showed only ischemic lesions. Nine patients showed acute ischemic lesions on magnetic resonance imaging (MRI) diffusion-weighted sequences that were not seen on the CT scan. Seven patients underwent both a CT scan and an MRI that showed ischemic lesions (on MRI diffusion-weighted and fluid attenuation inversion recovery sequences). The other 8 patients underwent an MRI that showed only acute ischemic lesions. Ischemic lesions were unique and multiple in 17 and 21 patients, respectively. Microbleeds were also observed on the MRI of 3 patients. Vertebrobasilar territory was involved in 29 patients (73%), along with anterior cerebral artery territory in 3 of them. The 11 other patients had supratentorial stroke with involvement of the medial cerebral artery, posterior cerebral artery, and both arteries in 7, 2, and 2 cases, respectively. Apart from a higher incidence of HTN in patients with supratentorial stroke (11/11 vs 16/29, p = 0.007), no difference was observed between patients with vertebrobasilar and supratentorial stroke. Among the 11 supratentorial strokes, 4 (37%) occurred after initiation of GC whereas the other 7 (63%) occurred at GCA diagnosis.

Neurovascular imaging was performed in 17 patients

(magnetic resonance angiography in 15, CT angiography in 1, and conventional cerebral angiography in 1). The procedure revealed vascular abnormalities in 14 patients, with a good correlation between the clinical picture and arterial involvement. Vertebrobasilar arteries were involved in 12 patients experiencing vertebrobasilar stroke (multiple stenosis in 9 and thrombosis in 3 others). In the 2 other patients with sylvian stroke, multiple vascular narrowing was observed on sylvian arteries along with intracranial carotid involvement. No isolated cases of cerebral vasculitis were observed.

Thirty-two patients (80%) underwent a Doppler ultrasound evaluation of the supraaortic arteries, which was abnormal in 20 cases (62%). In 10 patients, atherosclerotic plaques were observed in the extracranial carotid arteries without flow abnormalities. A halo (hypoechoic halo because of edema of the arterial wall) was also seen around the carotid arteries in 3 of them. In 4 other patients, including 3 with vertebrobasilar stroke and 1 with sylvian stroke, high-grade carotid stenosis (> 60%) was observed in extracranial carotid arteries. A halo was also apparent in the medial cerebral artery stroke patient. In the 6 remaining patients, including 5 with a vertebrobasilar stroke and 1 with sylvian stroke, vertebral arteries were involved (complete obstruction of 1 artery in 2 patients and both arteries in another 2 patients, multiple bilateral stenosis in 2 others).

Outcomes of patients with GCA-related stroke. All patients with stroke received GC [median dose: 58 (30–90) mg/day] at GCA diagnosis, including intravenous (IV) pulses in 18 of them. Thirty-one also received aspirin and 9 were prescribed anticoagulation therapy. During median followup of 44 months (6–176), 11 patients (28%) experienced disease relapse, occurring 12 months (1-48) after GCA diagnosis. Eleven patients (28%) died, including 7 within 5 days (2–13) of experiencing a stroke. Two patients died during GCA relapse with a repeat stroke 6 and 12 months postdiagnosis, respectively. Both patients were receiving aspirin. One patient died from myocardial infarction and 1 because of natural causes, but treatment had been discontinued in both cases. At the last visit, 17 patients had discontinued GC [median delay postdiagnosis: 23 mos (16–79)] and 12 were still receiving prednisone [5 mg/day (3–25)].

Disabilities persisted in 15 survivors (52%): focal deficit in 7, cognitive disorder in 8, cerebellar syndrome in 4, and blindness in 1 eye in 5 (secondary to acute anterior ischemic optic neuropathy in all patients).

Comparison of patients with and without stroke. Table 1 gives a detailed comparison of patients with and without stroke. Compared with the control group, the stroke patients were older [78 yrs (60–91) vs 74 yrs (50-94), p = 0.03], displayed more ophthalmic ischemic symptoms [25 (63%) vs 50 (25%), p < 0.001], had less anemia [22/37 (59%) vs 137/167 (79%), p = 0.03], and had a higher hemoglobin level at diagnosis [12.0 (9.4–16.1) g/dl vs 11.1 (7.8–15.8) g/dl, p = 0.02]. Conversely, PMR was less frequent [8 (20%) vs 76/198 (38%), p = 0.03] and biological inflammatory variables were lower at GCA diagnosis in patients with GCA-related stroke [ESR: 68 (10–119) mm vs 80 (10–140) mm, p = 0.003; CRP: 61 (28–185) mg/l vs 99 (6–400) mg/l, p = 0.04].

Regarding only patients with a positive TAB (Table 3), the same differences were observed. Patients with GCA-related stroke were older, had more ophthalmic symptoms at diagnosis, lower inflammatory variables, higher hemoglobin levels, and less anemia than control patients. In addition, there were more male patients in the stroke group (52% vs 31%, p = 0.02).

Multivariate logistic regression revealed that the best predictors for the occurrence of stroke were the presence of ophthalmic ischemic symptoms at diagnosis (OR 5, 95% CI 2.14–12.33, p = 0.0002) and the absence of anemia (OR 0.39, 95% CI 0.16–0.99, p = 0.04; Table 4).

Estimation of stroke incidence in the GCA population in each center. At Caen University Hospital, 17 out of 350 patients followed up for GCA were admitted to hospital with GCA-related stroke over a period of 20 years (1995–2015), which corresponds to an incidence rate of 4.5% in this center. In Dijon (152,000 inhabitants), a previous study indicated an incidence rate of 7%[5]. At Limoges University Hospital, over the last 20 years, 10 patients out of 335 patients with GCA had a GCA-related stroke, equivalent to an incidence rate of 3%. Finally, at Bichat University Hospital, 8 patients were referred for a GCA-related stroke out of a population of 191 patients followed up for 7 years (2009–2015). An incidence rate of 4.2% was recorded for this center.

DISCUSSION

Our study reports on a large cohort of patients with GCA-related stroke compared with a control group. The incidence rates of GCA-related stroke in our 4 centers ranged from 3% to 7%, which is consistent with published single-center and multicenter studies in different geographical areas[1,2,3,4,5,6,7]. In our cohort, we also found a close correlation between stroke and ophthalmic ischemic impairment, which was the most powerful predictive factor of stroke. We recorded a high mortality rate of 28% in patients with GCA-related stroke.

Most published series on cranial ischemic complications include patients with CVA and/or visual ischemic events, thus complicating the isolated analysis of patients with stroke. While ophthalmic ischemic symptoms are common and may concern 15% to 49% of patients with GCA at diagnosis[4,9,10,11], CVA are quite rare at diagnosis and may affect 2% to 7.5% of patients[1,2,3,4,6].

GCA-related cerebral ischemic events are more likely to affect the vertebrobasilar territory and concerned almost three-quarters of our patients, which is consistent with published data (50%–100%)[2,5,6]. Some ultrasonography studies highlighted the more frequent involvement of verte-

Table 3. Characteristics of 33 patients with GCA-related stroke and 134 control patients, all of whom have a positive temporal artery biopsy. Values are n (%) or median (range) unless otherwise specified.

Characteristics	Patients with Stroke, n = 33	Control, n = 134	p
Demographics			
Female/male, n	16/17	93/41	0.02
Age, yrs	78 (60–91)	74 (50–94)	0.03
CV risk factors			
Current smoker	12 (36)	26/129 (20)	0.05
Diabetes mellitus	8 (24)	15 (11)	0.05
Hypercholesterolemia	10 (30)	33 (25)	0.50
Hypertension	22 (67)	80 (60)	0.46
Coronary disease	5 (15)	14 (10)	0.45
≥ 2 CV risk factors	14 (42)	48 (36)	0.48
Anti-aggregation before GCA diagnosis	11 (33)	48 (36)	0.79
GCA characteristics			
Fever	8 (24)	36 (27)	0.76
Headaches	22 (67)	98 (74)	0.42
Abnormal temporal artery on physical examination	18 (55)	48/97 (49)	0.62
Scalp tenderness	13 (39)	43/99 (43)	0.68
Jaw claudication	13 (39)	50/101 (50)	0.31
Ophthalmic ischemic symptoms	21 (63)	33 (25)	< 0.001
Polymyalgia rheumatica	8 (24)	46/132 (35)	0.25
Erythrocyte sedimentation rate, mm*	68 (10–119)	80 (10–140)	0.02
C-reactive protein, mg/l	68 (28–185)	120 (6–400)	0.04
Fibrinogen, g/l	6 (4.5–9.77)	6.70 (3.70–11.46)	0.17
Hemoglobin, g/dl	12 (9.4–16.1)	11.2 (7.8–15.8)	0.006
Anemia	20/30 (67)	94/112 (84)	0.03
Platelets, g/mm^3	383 (99–957)	396 (126–913)	0.95

* Data available for 161 patients. GCA: giant cell arteritis; CV: cardiovascular.

Table 4. Variables associated with stroke in 240 patients with giant cell arteritis after univariate and multivariate logistic regression. OR were adjusted by the presence of cardiovascular risk factors (age, hypertension, hypercholesterolemia, diabetes, and smoking).

Variables	Univariate Analysis, OR (95% CI)	p	Multivariate Analysis, OR (95% CI)	p
Female	0.63 (0.32–1.26)	0.19		
Ophthalmic ischemic symptoms	4.93 (2.44–10.29)	< 0.0001	5 (2.14–12.33)	0.0002
Polymyalgia rheumatica	0.40 (0.16–0.88)	0.02		
C-reactive protein	1.006 (1.0006–1.01)	0.03		
Anemia	0.44 (0.21–0.95)	0.04	0.39 (0.16–0.99)	0.04

brobasilar territory in patients with GCA compared with control patients without GCA[12].

Vasculitis can involve the carotid and vertebral arteries as well as intracranial vessels. However, the involvement of intracranial arteries is quite uncommon because they contain little internal elastic lamina[13,14]. Conversely, vertebral and carotid arteries contain an internal elastic lamina from the aortic arch to their point of entry into the dura mater that may extend up to 5 mm intradurally[14,15]. Consequently, inflammatory processes are more likely to develop on such vessel segments, as observed in TAB.

In atherosclerosis-related stroke, the vertebrobasilar territory is affected in 15% to 20% of cases[16]. The occurrence of stroke in patients with active GCA challenges the characteristics of the vascular event, i.e., is it related to an inflammatory process or to atherosclerosis? Moreover, in the GCA population, many CV risk factors are often observed. The involvement of CV risk factors is controversial. Some authors discovered more CV risk factors in patients with severe cranial ischemic events[2,7], whereas others did not see any connection[4,17]. Our results did not show any significant differences regarding CV risk factors in patients with GCA-related stroke compared with the control group. Moreover, no differences were observed between the stroke patients and control group regarding the use of antiplatelet agents and anticoagulant therapy.

Overall, in the context of new GCA diagnosis, the occurrence of stroke is more likely to be linked to vasculitis as opposed to thromboembolic or cardioembolic disease, especially in patients with constitutional symptoms and/or acute-phase reactants.

Many studies identify some predictive factors of severe ischemic events, including CVA and ophthalmic ischemic symptoms. Interestingly, most of these studies such as ours observed more ischemic symptoms in patients with ophthalmic symptoms[2,4,11,16]. Male sex, HTN, history of ischemic heart disease, smoking, and previous cranial ischemic manifestations have also been linked with a higher risk of cerebrovascular events[2,4,7,9]. Patients with GCA-related ischemic events showed less frequent constitutional symptoms, lower levels of inflammatory variables, and higher hemoglobin levels than patients without ischemic events[2,4,7,16,18]. Obviously, patients with lower inflammatory variables are more likely to have higher hemoglobin levels.

We also found lower inflammatory variables and less anemia among our stroke patients[2,4,7,9]. Cid, *et al* also showed that patients with cranial ischemic events had lower ESR and higher hemoglobin levels[9]. This is consistent with reduced levels of interleukin 6 (IL-6), a key cytokine in GCA pathogenesis, in cases of GCA–related ischemic symptoms[19,20]. Moreover, proinflammatory cytokines (IL-1β, IL-6, tumor necrosis factor-α) produced locally in inflamed arteries may have a potent biological effect on endothelial and smooth muscle cells, such as procoagulant activity, neovascularization, matrix deposition, myointimal cell proliferation, and vascular tone regulation[9,21,22]. Regulation of inflammation may thus affect endothelial cells and modulate vascular response.

The absence of relevant controlled treatment trials in this rare setting does not allow for standard recommendations to be defined. The administration of high-dose oral prednisone (1 mg/kg/day) in patients with GCA-related complications is accepted. IV infusion of high-dose methylprednisolone (15 mg/kg for 1 to 3 days) is widely practiced, although its superior efficacy is not clearly demonstrated[23]. Several observations also describe the administration of concomitant immunosuppressants in this context[3]. Some authors suggest prescribing antiplatelet agents and low molecular weight heparin at GC onset[6,17,24]. Moreover, as in our study, many strokes occur within a few days/weeks of GC onset, which suggests that GC may lead to the release of thrombi in inflamed vessels that may embolize to more distal parts of the vessel and trigger their occlusion[16]. The protective effect of antiplatelet agents or anticoagulants in this setting is not obvious and remains controversial[2,24,25].

Our study has notable strengths, especially the large number of patients enrolled, which is over 4× higher than that of any other published case series[1,2,3,4,5,6,7]. The comparison of stroke patients to a large control group allowed us to demonstrate significant differences in terms of clinical value. Further, we included only patients with CVA, regardless of ophthalmic involvement, whereas a few other series included patients with severe ischemic symptoms (i.e., CVA and/or visual ischemic impairment). However, some limitations must be discussed. First, the retrospective design of our study did not facilitate complete data retrieval for all patients, especially in the control group. Little information was available on longterm outcomes in the control group, precluding any comparative analysis on mortality. Second, we included only patients with stroke and persistent neurologic events. Our study did not include other cerebrovascular events such as transient ischemic attack or multiinfarct dementia, which are other indicators of brain vessel involvement. We therefore probably underestimated the frequency of neurological events in GCA. Third, our control patients were not matched to our patients with stroke, which limits the interpretation of certain findings that we observed, such as age differences. Finally, with the methodology we used to calculate GCA-related stroke incidence rates in each center, we cannot rule out the possibility of having missed cases (except in Dijon Hospital[5]). However, incidence rates in each center were relatively homogeneous.

Stroke is a rare and severe ischemic complication that may develop in patients with recently diagnosed GCA. It is more likely to occur in the vertebrobasilar territory and in patients who experience ophthalmic ischemic symptoms with low inflammatory variables. Treatment relies on GC and at least longterm antiplatelet agents, because stroke can occur within a few days or weeks of GC onset. Therefore, further prospective studies are still required to define the involvement of anticoagulants and IV methylprednisolone bolus medication in this setting.

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