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Running title: Stroke in Takayasu arteritis

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Highlights

Takayasu arteritis is a rare cause of stroke, especially in young adults.

Stroke in Takayasu arteritis may occur after carotid artery surgery.

Stroke is a major cause of disability in Takayasu arteritis.

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PC and FCA conducted the statistical analysis.

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Abstract

Objectives: Takayasu arteritis **(TA**) is a giant cells arteritis usually affecting young women and characterized by inflammatory and ischemic signs of large vessel involvement, including extracranial cerebral arteries. The impact of stroke on TA prognosis has not been well evaluated.

Methods: We performed a retrospective multicenter review of patients with definite TA who experienced at least one stroke and compared the findings to 17 matched patients with TA diagnosis without neurological involvement.

Results: Seventeen patients (15 women, median age at stroke diagnosis 44 years) receiving a diagnosis of TA and stroke between 2002 and 2016 in our institution were included, from a cohort of 126 patients suffering from TA (13.5%). At diagnosis, patients from both groups had comparable cardiovascular risk factors. The first cerebrovascular event was ischemic stroke (n = 15) or transient ischemic attack (n = 2). In 8 patients, stroke occurred after the TA diagnosis was made. In 4 patients, stroke occurred after carotid surgery. At the end of follow-up, 59% of patients had a neurological impairment, 35% had a recurrence of stroke, and 24% suffered from epilepsy.

Conclusions: Stroke is a major cause of disability in TA patients. Internal carotid surgery may be performed with caution because of the risk of stroke after the procedure.

Abstract word count 212

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

	Patients with TA and stroke (N = 17)	**Controls (TA without stroke) (N = 17)**
Median age at diagnosis (years [range])	45 [15-70]	39 [15-65]
Median age at first stroke (years)	44	-
Male/Female	2/15	2/15
Median follow up (month [range])*	137 [27 – 294]	73 [17-417]
Cardiovascular disease risk factors		
- **Smoking (median pack-years [range])**	7 [0-40]	5 [0-40]
- **Dyslipidemia**	4 (23.5%)	4 (23.5%)
- **Hypertension**	8 (47.0%)	6 (35.3%)
- **Diabetes mellitus**	2 (11.8%)	3 (17.7%)
- **Coronaropathy**	1 (5.9%)	1 (5.9%)
- **BMI (median [range])**	25 [14.8 - 30.2]	23,3 [14.8 – 32.7]
- **Familial history of MI or stroke**	1 (5.9%)	1 (5.9%)
- **Peripheral artery disease**	1 (5.9%)	0
Symptoms at diagnosis		
- **Upper limb claudication**	4 (23.5%)	6 (35.3%)
- **Lower limb claudication**	4 (23.5%)	1 (5.9%)
- **Difference in SBP between arms > 10 mmHg**	11 (64.7%)	12 (70.6%)
- **Painful carotid**	2 (11.8%)	4 (23.5%)
- **Decreased brachial artery pulse**	9 (53.0%)	10 (58.8%)
- **Bruit over subclavian or carotid arteries**	12 (70.6%)	14 (82.4%)
- **Bruit over femoral arteries**	2 (11.8%)	3 (17.7%)
- **Cardiac murmur**	6 (35.3%)	5 (29.4%)
- **Fever**	1 (5.9%)	4 (23.5%)
- **Loss of weight**	2 (11.8%)	4 (23.5%)
Laboratory tests at diagnosis		
- **Median ESR (mm/h [range])**	50 [4-100]	27,5 [5-52]
- **Median CRP (mg/L [range])**	40 [4-93]	6 [2-180]
Imaging data at diagnosis		
- **Internal carotid stenosis***	**13 (76.5%)**	**4 (23.5%)**
- **Vertebral arteries stenosis**	5 (29.4%)	5 (29.4%)
- **External carotid stenosis**	4 (23.5%)	4 (23.5%)
- **Subclavian arteries stenosis**	15 (88.2%)	12 (70.6%)
- **Aortic aneurysm**	5 (29.4%)	4 (23.5%)
- **Renal arteries stenosis**	6 (35.3%)	6 (35.3%)
- **Visceral arteries stenosis**	6 (35.3%)	7 (41.2%)
Death	2 (11.8%)	1 (5.9%)
Median survival (month, [range])	41 [2 -229]	73 [17-417]
Carotid surgery	6 (35.3%)	2 (11.8%)
Surgical re-intervention on carotid	3 (17.7%)	0

TA: Takayasu arteritis; BMI: body mass index; MI: myocardial infarction; SBP: systolic blood pressure; ESR: erythrocyte sedimentation rate; CRP: C-reactive protein; * $p < 0,05$.

Table 2. Characteristics of stroke in Takayasu arteritis patients.

Stroke features	Patients with stroke N = 17
Symptoms	
- Headache	4
- Aphasia	5
- Hemiparesis	10
- Cerebellar ataxia	1
- Visual loss	4
- Diplopia	3
Transient ischemic attack	2
Ischemic stroke	15
NIHSS at admission (mean [range])	4 [0-18]
Stroke after surgery	4
Co-occurrence of stroke and TA diagnosis	4
Diagnosis of TA before stroke	8
Diagnosis of stroke before TA	5
Involved territory	
- Anterior cerebral artery	4
- Middle cerebral artery	12
- Posterior cerebral artery	0
- Cerebellar artery	1
Multiple infarcts	3
Treatment before stroke	
- Corticosteroids	5
- Statin	5
- Antiplatelet therapy	9
- Immunosuppressor	2
Treatment after stroke	
- Thrombolytic therapy	3
- Antiplatelet therapy	17
- Anticoagulant	3
- Statin	13
- Corticosteroids	17
Median dose (mg)	30
High dose intravenous steroid therapy	6
- Methotrexate	7
- Tocilizumab	2
Outcomes	
- Neurological impairment	10
- Stroke recurrence: one relapse	4
- Stroke recurrence: two relapses or more	2
- Epilepsy	4
- Cognitive impairment	1
- Final Barthel score (median [range])	85 [70-100]
- Median final CRP (mg/L [range])	5 [0 -18]
Median time between two strokes (range)	10 [2-25]

NIHSS: National Institute of Health Stroke Scale; TA: Takayasu arteritis; CRP: C-reactive protein.

Takayasu arteritis **(TA**) is a giant cells arteritis usually affecting young women and characterized by inflammatory and ischemic signs of large vessel involvement. The aorta and its large arterial branches are typically involved in TA and may lead to coronary artery disease, renovascular hypertension, intestinal ischemia and/or stroke [33]. Vascular involvement is usually associated with an inflammatory state with an increased erythrocyte sedimentation rate (**ESR**) and/or C-reactive protein (**CRP**). Internal carotid artery (**ICA)** involvement is uncommon, and intracranial arteries are exceptionally affected [2, 6]. The occurrence of strokes during TA is estimated to be between 10 and 20%, and a more recent meta-analysis found a prevalence of 15.8% [11, 36]. However, the impact of stroke on prognosis in TA patients has not been well evaluated.
We thus conducted a retrospective, case-controlled study with an updated review of the literature, to evaluate the prognosis of cerebrovascular events in TA and to characterize the clinical and imaging presentation.

Patients and Methods

Patients' selection

We performed a retrospective study in the Departments of Internal Medicine and Neurology of a French University hospital. Patients who received a definite diagnosis of TA according to the American college of rheumatology criteria [3] and who experienced a cerebrovascular event were identified through the computerized local database (Programme de Médicalisation des Systèmes d'Information, **PMSI**). Only patients in whom the cerebrovascular event occurred at diagnosis or during the evolution of TA were included. For patients in whom TA diagnosis was made after stroke occurrence, 2 independent medical doctors reviewed the medical records, and the patients were finally included if the stroke was obviously related to the TA. All forms of cerebrovascular events were considered, including transient ischemic attacks (TIA), hemorrhagic and ischemic strokes. 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 TA diagnosis and were sex-matched in a 1:1 ratio with patients of the group “cerebrovascular event”.

Data collection

The characteristics of all patients were obtained through medical records. A standardized form was used to collect data for all cases, including demographics (age and sex), date of TA diagnosis and cerebrovascular event, and cardiovascular risk factors (smoking, diabetes mellitus, hypertension, hypercholesterolemia and family history). Clinical data (headache, visual impairment, upper and lower limb claudication, asymmetric blood pressure, painful carotid, vascular murmur and fever), biological data at diagnosis of TA (ESR, CRP, fibrinogen, gamma-glutamyl transferase (**GGT**) hemoglobin and platelet count) and imaging studies (magnetic resonance imaging (MRI), ^{18} fluorodesoxyglucose (^{18}**FDG**) positron emission tomography (**PET**)-scan if available) were collected for all patients as well as treatments received at diagnosis of TA and at the time of the first cerebrovascular event.

All stroke characteristics were recorded, including clinical features and cerebral MRI findings.

Statistical analyses

Data are presented as median (range) for continuous variables and number (%) for qualitative variables. Differences between groups were tested using the Mann-Whitney test for continuous data and Fisher exact test for qualitative data. All tests were two-sided, and a p-value < 0.05 was considered statistically significant. The statistical analyses were performed using commercially available software (IBM SPSS for Windows).

Results

Patients' characteristics at TA diagnosis

Seventeen patients who received a diagnosis of TA and stroke between 2002 and 2016 in our institution were included, from a cohort of 126 patients suffering from TA (13.5%). We enrolled 17 controls with TA who were sex matched and had no neurological signs. There were 15 women (88%) and 2 men (12%) in each group. The median duration of follow-up was 137 months (27 - 294) in the stroke group and 73 months (17- 417) in the control group.

The baseline characteristics of the patients are detailed in **Table 1**.

At diagnosis, patients from both groups had comparable cardiovascular risk factors. There were no significant differences in terms of smoking, diabetes mellitus, peripheral artery disease, body mass index (**BMI**), coronaropathy or familial history of cardiovascular and cerebrovascular event frequencies. Hypertension was more frequently observed in the stroke group (47 versus 35%) compared to the controls, although this difference was not statistically significant.

The clinical presentation of TA at diagnosis was similar in the 2 groups.

The median blood CRP level at TA diagnosis was higher in patients with cerebrovascular events than in control patients (40 and 6 mg/L respectively), but the difference was not statistically significant. Other biological markers of inflammation at TA diagnosis, namely, ESR, hemoglobin and fibrinogen levels, were similar in the two groups.

Interestingly, imaging data revealed more ICA stenosis in patients with stroke than in controls (76,5% versus 23,5%; p = 0.005). The other vascular territories were similarly involved in the 2 groups.

Characteristics of the cerebrovascular events and outcomes

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

The first cerebrovascular event was ischemic stroke (n = 15) or TIA (n = 2). There were no hemorrhagic strokes. Stroke occurred with a typical presentation: hemiparesis in 53% of patients,

aphasia in 29%, visual impairment in 24% and cerebellar ataxia in 6%. The median National Institutes of Health Stroke scale score (**NIHSS**) on admission was 4 (ranging from 0 to 18).

Most cerebrovascular events were located in the ICA, especially in the middle cerebral artery (**MCA**) territory (n = 12, 71%) and the anterior cerebral artery (**ACA**) territory (n = 4, 24%), whereas one event (6%) was located in the cerebellar artery territory, and none were in the posterior cerebral artery territory. Three patients (18%) had multiple infarcts, mostly in the same vascular territory, which was the carotid territory in all cases of multiples strokes.

Cerebrovascular events occurred in 8 patients suffering from previously diagnosed TA with a median delay of 13 years (ranging from 1 to 21) after TA diagnosis. In 4 patients, stroke occurred after carotid surgery. Stroke was the first symptom of TA in 9 patients (53%). The TA diagnosis was confirmed with a median duration of 2 years (ranging from 0 to 12 years). In 4 cases, stroke and TA were concomitantly diagnosed.

All strokes were considered linked to the disease because of high CRP levels, suggestive imaging results, and exclusion of cardioembolic or atherosclerotic causes.

It is worth noting, that at the end of follow-up 59% of the patients had a neurological impairment, 35% had a recurrence of stroke and 24% suffered from epilepsy. These neurological sequelae had an impact on the patients' autonomy since the median final Barthel score was still below 100 at the end of follow-up. Two patients died, and the median survival rate was 41 months.

Discussion

Stroke is an important feature of TA, occurring in at least 15.8% of cases [11, 32, 44]. It has a variable presentation [5, 6, 29-31, 38]. Stroke or TIA may be the first sign of the disease, in a variable percentage ranging from 9% to 93% [17, 25, 37, 42, 46, 47]. We found that cerebrovascular events revealed TA in 53% of cases. Among these cases, the diagnosis of TA was

confirmed with a median delay of 2 years, which may have resulted in delayed treatment of the arteritis. Interestingly, we found that stroke occurred after carotid surgery in 4 cases.

Mechanisms of stroke in TA

The underlying mechanisms of ischemic strokes in TA remain unclear. Various mechanisms have been described: vascular occlusion secondary to arterial thrombosis and vasculitis [11, 22, 35], carotid aneurysm [7], embolism from aortic regurgitation, hemodynamic origin due to tight stenosis or vascular steal [24], vasospasm in hypertensive encephalopathy [8] or rarely, carotid artery dissection [14], distal carotid stump embolism [20] or moyamoya disease [43]. In our series, patients with stroke had significantly more ICA stenosis than controls. Almost all patients had a stroke in ACA or MCA territories, and only 3 strokes were in border-zones, whereas the others were large lobar infarctions. Contrast-enhanced ultrasonography may help to detect active vascular inflammation in TA [15]. In a recent American study including 79 patients, 11.4% patients presented with acute ischemic stroke: 6.3% with TIA and 1.3% with symptomatic intracranial hemorrhage [6]. Vascular imaging showed that 22.8% of patients had narrowing of the ICA; the right ICA was affected more often than the left, and all patients with ICA involvement also had common carotid artery stenosis. The authors hypothesize that ICA stenosis in TA could be secondary to inflammatory vasculitis more than the result of prior embolization, because 6 patients had multifocal stenosis, suggestive of a vasculitis etiology. In contrast, Kumral et al. found that 25% of patients with ischemic stroke presented with micro-embolus during transcranial doppler sonography monitoring, suggesting an embolic mechanism in the pathogenesis of stroke in TA [26].

A recent study found that lupus anticoagulant or a diagnosis of antiphospholipid syndrome were found in 45% of TA patients in a retrospective cohort of 22 patients; lupus anticoagulant was associated with a higher prevalence of cerebrovascular events [19]. In our cohort, 2 patients had an antiphospholipid biology and one immunoglobulin IgM anticardiolipin antibodies without

criteria for an antiphospholipid syndrome. No patients in the control group had antiphospholipid or anticardiolipin antibodies. The number of patients is too small to make a conclusion regarding the impact of antiphospholipids antibodies on cerebrovascular risk. Other hypercoagulability states have also been associated with stroke in TA [40].

Stroke and cardiovascular risk in TA

Concerning risk factors of stroke in TA, a French retrospective study revealed that Maghreb patients had significantly more stroke than European patients [4]. The geographical origin did not differ in our series between the 2 groups. Ringleb et al. also suggested that TA presented with similar cerebrovascular signs in Europe and Japan [39]. Women may have more neurological involvement since female patients with TA have more frequent involvement of the thoracic aorta and its branches, whereas involvement of the abdominal aorta and its branches is more common in males [27]. Since the number of cases of stroke in TA is low, it is difficult to make a conclusion regarding female predominance.

A previous study showed that anemia and low body mass index (**BMI)** were associated with increased cardiovascular disease in patients with TA [28]. Our study did not find the same results, since BMI and hemoglobin were not different in the “stroke” and the “control” groups. Lastly, as in our series, a Korean study found that the conventional stroke risk factors, ESR and CRP, did not differ significantly between the stroke and control groups [18].

In a Chinese study, neurological features in patients with TA were variable and correlated with the number of arteries and the site of involvement. Resistant hypertension was one of the most important risk factors for hemorrhagic stroke in patients with TA [48]. We also observed more hypertension in the “stroke” group, although the difference was not statistically significant.

Treatments and outcomes

Treatments in TA usually include low-dose aspirin, anti-inflammatory medications (corticosteroids, frequently associated with immunosuppressive drugs). Recently, biologics in TA have been increasingly used [1, 9], especially in cases of stroke [34]. In our series, 2 patients received tocilizumab, whereas 7 received methotrexate. Stroke may also occur during infliximab treatment [21]. Due to the rarity of TA-associated strokes, it is difficult to give evidence-based recommendations on the use of biologics in this setting.

Our patients had neurological sequelae in 59% of cases. Paula et al. found the same important morbidity: 12 of 18 (66.7%) patients developed neurological impairments [10]. In this study, one patient died as a result of cerebral hyperperfusion after carotid surgery. In our series, 24% of strokes occurred after vascular surgery, and 35% of patients required a carotid revascularization, sometimes twice. Fields et al. reported that operated patients with active TA were more likely to develop thrombosis or restenosis [12]. Thus, we recommend that surgical interventions may be achieved when the disease is quiescent [13, 41]. Stent placement may also be used [16], although intra stent thrombosis may occur [45], possibly due to increased inflammation of the arterial wall.

Limitations

Our study has several limitations: it is a retrospective study with memory bias. The patients were likely to suffer from a more severe disease spectrum since they were treated in a tertiary care center. In addition, finally, imaging analysis was not uniformly performed because vascular involvement was investigated with different types of vascular imaging studies (CT-scan, MRI or sonography), each with its own limitations [23, 49].

Conclusions

The occurrence of stroke during TA may be the first sign of the disease or may occur during follow-up, especially after vascular surgery. Stroke is associated with high morbidity since 60% of patients sustain neurological impairment, and recurrence occurs in 35% of cases. This is the major finding

of this study which shows that stroke occurrence in TA impact the outcomes and in particular neutrological disability. The occurrence of stroke during TA is associated with the presence of ICA stenosis. A systematic evaluation of intracranial vascularization should be performed in this setting.

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