Clinical and vascular features of stroke in Takayasu's arteritis: A 24-year retrospective study

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Abstract

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Objective: To investigate the clinical characteristics, vascular imaging features, and prognosis of Takayasu's arteritis (TA) patients with stroke in China.

Methods: Medical charts of 411 in-patients who fulfilled the classification criteria of modified 1990 American College of Rheumatology (ACR) criteria for TA and with complete data from 1990 to 2014 were reviewed retrospectively. The demographic data, symptoms and signs, laboratory test results, radiological features, treatment, and interventional or surgical procedures were collected and analyzed. Patients with radiological confirmed stroke were identified. Chi-square test or Fisher exact test was used to compare the differences between patients with and without stroke.

Results: Twenty-two patients with ischemic stroke (IS) and 4 patients with hemorrhagic stroke were identified. The incidence of stroke in TA patients was 6.3% (26/411), of which 11 patients were considered to be the initial manifestation. Stroke patients had more visual acuity loss (15.4% vs. 4.7%, P = 0.042). Systemic inflammatory symptoms and inflammatory markers were less common in patients with stroke than in those without stroke [fever P = 0.007; erythrocyte sedimentation rate (ESR) or C-reactive protein (CRP), P < 0.001]. Cranial angiography showed that common carotid artery (CCA) (73.0%, 19/26) and subclavian artery (SCA) (73.0%, 19/26) were the most involved, followed by internal carotid artery (ICA) (57.7%, 15/26) in stroke patients. The intracranial vascular involvement rate of stroke patients was 38.5% (10/26); the middle cerebral artery (MCA) was the most common artery involved. The most common site of stroke was the basal ganglia region. The occurrence of intracranial vascular involvement was much higher in patients with stroke when compared to patients without stroke (38.5% vs. 5.5%, P < 0.001). Among all patients with intracranial vascular involvement, patients without stroke received more aggressive treatment than patients with stroke (90.4% vs. 20.0%, P < 0.001). There was no significant increase in in-hospital mortality in patients with stroke compared with patients without stroke (3.8% vs. 2.3%, P = 0.629).

Conclusion: Stroke is the initial presentation in 50% of TA patients with stroke. The intracranial vascular involvement rate is significantly increased in stroke patients than in patients without stroke. The artery invloved in patients with stroke are cervical artery and intracranial involvement. Systemic inflammation is less in patients with stroke. Aggressive treatment for TA with glucosteroid (GC) and immunosuppressive agents combined with anti-stroke therapy is needed to improve the prognosis of TA complicated stroke.

Keywords

cervical artery • intracranial artery • stroke • Takayasu's arteritis

Introduction

Takayasu's arteritis (TA) is a systemic inflammatory

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vasculitis with unknown etiology. It mainly affects aorta and its major branches.^[1] Clinical manifestations include systemic inflammatory symptoms, e.g., fever, weight loss, discomfort, and symptoms and signs resulting from vascular dysfunction.^[2] More than 50% of patients with TA may have neurologic manifestations, including headache, dizziness, syncope, amaurosis fugax, stroke, and transient cerebral ischemia (TIA). ^[3] Neurological manifestations of TA may relate to intracranial or extracranial vascular involvement due to steno-occlusive lesions and/or shifting of blood flow.^[4, 5] However, the most threatening neurological damage of TA is stroke, which is a major cause of disability in TA patients, although it is rare. So far, little is known about the prevalence of stroke and its related clinical features as well as vascular involvement among these patients. In this study, we reported a retrospective study of 411 Chinese patients of TA with a particular focus on stroke.

There is a large number of TA patients in China, but there are few studies on TA stroke. And there may be some bias among the cohort studies. In this study, we report a retrospective study of 411 Chinese TA patients in our center, with a particular focus on stroke. Clinical differences were compared between stroke and non-stroke patients. The clinical course, cervical and intracranial artery involvement, and prognosis of ischemic and hemorrhagic stroke were described in detail. There is the first analysis compared the clinical differences between stroke and non-stroke patients with intracranial artery involvement. We hope this study might help clinicians to better understand the cerebrovascular events in TA patients.

Methods

Ethical Approval

This retrospective study was approved by the Ethics Committees of hospital and was conducted in accordance with the Declaration of Helsinki. Informed consent was waived because of the retrospective nature of the study.

Patients

Four-hundred-and-eleven patients with complete data from 1990 to 2014 were included in this study. All patients fulfilled the classification criteria of modified 1990 American College of Rheumatology (ACR) criteria.^[6] All patients had undergone digital subtraction angiography (DSA) or carotid and aortic computer tomography angiography (CTA) examinations.

All cerebrovascular events were included and analyzed, including TIA, hemorrhagic stroke, and ischemic stroke (IS). Stroke was defined as an episode of acute neurological dysfunction presumed to be caused by ischemia or hemorrhage, persisting \geq 24 h or until death. IS was defined as an episode of neurological dysfunction caused by focal cerebral, spinal, or retinal infarction. Cerebrovascular events related to atrial fibrillation or overt atherosclerotic lesions were excluded. Hemorrhagic stroke was defined as the stroke caused by intracerebral hemorrhage (ICH) or subarachnoid hemorrhage (SAH).^[7] TIA was defined as brief episodes of neurological dysfunction resulting from focal cerebral ischemia not associated with permanent cerebral infarction.^[8]

Data Collection

The demographic data, clinical presentations, physical examination findings, laboratory tests, radiological features, angiographic involvement patterns, treatment, and interventions or surgical procedures were collected and analyzed. The angiographic involvement pattern was based on the 1996 Numano criteria.^[6] A database file was built for data collection and all the data were entered by 4 junior rheumatologists and then checked by 1 senior rheumatologist with Epidata (Version 3.1, Beijing Health Cloud Technology Company Limited, Beijing, China). Data were exported to statistical product and service solutions (SPSS) software (version 23.0, IBM SPSS statistics, Armonk, New York, USA) for further analysis.

Statistical Analysis

Numerical data were expressed as mean \pm standard deviation (SD) or median (range: min–max), while categorical data were expressed as percentages or numbers. Numerical data were compared using the independent sample *t* test or one-way analysis of variance (ANOVA) analysis followed by the least significant difference (LSD) comparison method. Categorical data were compared using Chi-square test or Fisher exact test, as appropriate. A two-sided *P* value < 0.05 was considered statistically significant. Analysis was performed with SPSS software.

Results

Clinical Features of TA Patients with or without Stroke

In the 411 TA patients, 26/411 patients (6.3%) had stroke. Twenty-two patients were diagnosed as IS and 4 patients as hemorrhagic stroke, including 2 patients with ICH and 2 patients with SAH. The mean age of disease onset was 20.5 ± 8.5 years. Among the 22 patients with IS, 16 were female and 6 were male. The 4 hemorrhagic stroke patients consisted of 3 females and 1 male. Stroke was the initial manifestation of TA in 42.3% (11/26) of patients. Numano type V vascular involvement (61.5%) was the most common vascular type, followed by type I (30.8%). Inflammatory systemic features such as fever and weight loss were found in 4 patients before stroke. Other neurological presentations besides stroke of the stroke group were not significantly different from patients without. Nine (34.6%) patients with stroke developed ocular symptoms. The general characteristics of patients with or without stroke are listed in Table 1.

The proportion of male patients was higher in the stroke group when compared with 385 TA patients without stroke, but without statistical significance. There was no difference in the age of disease onset and angiographic classification pattern. Fever was less common in patients with stroke than in patients without (P < 0.05). Meanwhile, patients with stroke had lower levels of erythrocyte sedimentation rate (ESR) ($15.3 \pm 13.3 \text{ mm/h}$ vs. $34.0 \pm 34.6 \text{ mm/h}$, P < 0.001) and serum C-reactive protein (CRP) ($6.8 \pm 11.1 \text{ mg/L}$ vs. $39.0 \pm 60.6 \text{ mg/L}$, P < 0.001). Patients with stroke had lower peripheral white blood cell count ($7.9 \pm 2.3 \times 10^9$ /L vs. $9.0 \pm 3.6 \times 10^9$ /L, P = 0.026) and platelet count ($288.7 \pm 110.0 \times 10^9$ /L vs. $327.0 \pm 127.4 \times 10^9$ /L, P = 0.004),

Table 1: General characteristics of 26 stroke patients and 385 patients without stroke of TA

	Stroke (<i>N</i> = 26)		Without stroke		
	IS (<i>N</i> = 22)	SAH + ICH (N = 4)	(N = 385)	P value	
Female/male	19/7	(2.7:1)	308/77 (4:1)	0.397	
Age at onset (years)	25.0	± 8.5	24.6 ± 9.6	0.798	
Duration of disease at first admission (months)	33.3	± 40.3	50.1 ± 83.4	0.286	
Angiographic clas- sification	10/0	1 50()	224 (60.09())	0.020	
V IV III IIa IIb I	1 (4 1 (4 8 (3)	.5%) .5%) D.8%)	26 (6.8%) 12 (3.1%) 15 (3.9%) 15 (3.9%) 83 (21.6%)	0.939 0.171 0.361 0.990 0.990 0.274	
Constitutional symptoms					
Fever	2/	26	126/385	0.007	
Malaise	4,	26	118/385	0.122	
Weight loss	4,	/26	78/385	0.800	
Cardiovascular risk factors					
Hypertension	14	/26	197/385	0.687	
Diabetes mellitus		0	3/385	1.000	
Smoking					
history of smoking	0/	/26	10/385	1.000	
Current smoker	2/	26	13/385	0.559	
Vascular findings					
Asymmetric blood pressure in limbs	14	/26	229/385	0.520	
Asymmetric pulsation	10	/26	148/385	1.000	
bruits in neck area	18	/26	258/385	1.000	
Claudication					
Upper limbs	7,	26	55/385	0.563	
Lower limbs	7,	/26	50/385	0.071	
Renal abnormalities					
Renal artery involvement	10	/26	191/385	0.314	
Neurological mani- festations					
Headache	9/	26	116/385	0.662	
Syncope	3/	26	46/385	1.000	
Dizziness	12	/26	159/385	1.000	
Amaurosis fugax	5,	26	55/385	1.000	
Epileptic seizure	0/	/26	12/385	0.097	
Ocular manifestation					
Blurred vision	5,	26	99/385	0.131	
Vision loss	4/26 (15.4%)	18/385 (4.7%)	0.042	
Defect of visual field		0	9/385	1.000	

24

Table 1: Continued

	Stroke	(N = 26)	Without stroke		
	IS (<i>N</i> = 22)	SAH + ICH (N = 4)	(N = 385)	P value	
Blindness	0		9/385	1.000	
Ophthalmoscope findings					
Hypertensive retinopathy	0/	/9 [#]	23/156#	0.363	
TA-related retinopathy	9/	/9 [#]	23/156#	<0.001	
Laboratory variables					
ESR (mm/h)	15.3 ± 13.3		34.0 ± 34.6	<0.001	
hs-CRP (mg/L)	14.6 ± 46.4		15.4 ± 28.7	<0.001	
CRP (mg/L)	6.8 ± 11.1		39.0 ± 60.6	<0.001	
WBC (109/L)	7.9 ± 2.3		9.0 ± 3.6	0.026	
Hgb (g/L)	122.6 ± 18.7		118.0 ± 23.0	0.032	
PLT (109/L)	288.7 ±	110.0	327.0 ± 127.4	0.004	
LDL (mg/L)	2.5 ±	1.5	2.7 ± 0.9	0.442	
Intracranial vascular involvement	r 10/26 (38.5%)		21/385 (5.5%)	<0.001	
mortality 1/26 (3.8%)			9/385 (2.3%)	0.629	

⁴Actually detected. TA, Takayasu's arteritis; CRP, C-reactive protein; ESR, cyte sedimentation rate; Hgb, hemoglobin; hs-CRP, high sensitive C-reactive protein; ICH, intracerebral hemorrhage; IS, ischemic stroke; LDL, low-density lipoprotein cholesterol; SAH, subarachnoid hemorrhage; WBC, white blood cell.

but higher level of hemoglobin (Hb, 122.6 ± 18.7 g/L vs. 118.0 ± 23.0 g/L, P = 0.032) than patients without stroke. There was no difference between the stroke group and the non-stroke group in other neurological symptoms, including headache, syncope, dizziness, amaurosis fugax, and seizure. However, the incidence of vision loss was much higher in patients with stroke than in patients without stroke (15.4% vs. 4.7%, P = 0.042). Notably, the incidence of intracranial vascular involvement was much higher in patients with stroke (38.5% vs. 5.5%, P < 0.001) than in patients without.

Subgroup Analysis for Stroke in TA

The 26 stroke patients could be divided into 4 groups according to the initial presentation and the causes of stroke: 10 patients had stroke as the initial symptom (the IS-initial subgroup), 12 patients' initial presentation did not involve stroke (the non-initial IS group), 2 patients presented with stroke that was complicated with subarachnoid hemorrhage (the SAH group), and there were 2 patients whose stroke was caused by intracerebral hemorrhage (the ICH group). Among the IS-initial subgroup, they were hospitalized with stroke (Hemiplegia and/or aphasia, 4/10) or the stroke was prophased by TIA (4/10), syncope (1/10), and ophthalmalgia (1/10), followed by persistent hemiparesis and speech disturbance. In the non-initial IS group, there were patients

(Continued)

who had TA for $30.2 \pm 31.0 (3-96)$ months before the onset of stroke. Two of the SAH patients were diagnosed with TA due to dizziness or claudication, and SAH developed about 4–5 years later. One ICH patient had a sudden ICH as the initial clinical manifestation. The other ICH patient, whose initial clinical manifestations were hypertension and amaurosis, developed ICH 16 years later. There was no difference in the gender and age of disease onset among the 3 groups, but patients with hemorrhagic stroke experienced a longer duration from disease onset to the event (P < 0.05). Some patients had inflammatory presentations before stroke, but no difference was shown between the 3 groups.

According to the examination of magnetic resonance imaging (MRI) results, basal ganglia was the most common location of stroke (59.0%), followed by multiple lobes (frontal lobe, temporal lobe, parietal lobe, and insula). All the 26 stroke patients had completed the extracranial and intracranial vascular DSA or CTA examination. According to the vascular involvement and image findings, the causes of IS for most patients were stenosis of cervical vessels and/or intracranial vessel; only 1 patient's stroke was caused by cerebral embolism, which was secondary to the dissociation of the aortic arch thrombi,

and 1 patient had IS immediately after carotid surgery. Two patients with ICH had refractory severe hypertension due to renal artery involvement. Both patients with SAH had no clear cause (Table 2).

Characteristics of Cervical and Intracranial Vascular Lesions in Patients With or Without Stroke

Cervical and Intracranial Artery Involvement in Patients with and without Stroke

Cervical vascular examination of 26 stroke patients showed that all patients had cervical vascular involvement. The most commonly involved were common carotid artery (CCA) and subclavian artery (SCA), followed by internal carotid artery (ICA). Most of these arteries were stenotic or obliterated and dilated. Ten out of 26 patients (38.5%) had intracranial artery involvement revealed by vascular examination. The middle cerebral Artery (MCA) was the most frequently involved with an involvement rate of 76.9% (10/13). In most patients, the artery was occluded rather than stenosed (Table 3 and Figure 1).

Table 2: Characteristics of patient with IS and SAH + ICH

	IS (N	= 22)	SAH + ICH (<i>N</i> = 4)	P value	
-	Initial (<i>N</i> = 10)	Non-initial (N = 12)			
Female/male	8/2	8/4	3/1	0.778	
Age at onset (years)	23.0 ± 5.5	23.8 ± 9.1	27.2 ± 14.3	0.718	
Duration (from disease onset to stroke, months)	0.0 ± 0.0 (0)	30.2 ± 31.0 (3–96)	73.8 ± 82.8 (0–192)	0.008	
Initial symptom	TIA (4) Syncope (1) Ophthalmalgia (1) Stroke (4)	Dizziness (7) Pulseless (2) Claudication (2) Carotidynia (2) Fever and myalgia (2) Arthralgia (1)	Hypertension and Amaurosis (1) Hypertension and ICH (1) Claudication (1) Dizziness and Claudication (1)		
Elevated ESR/CRP levels	2/5	3/8	2/2	0.916	
GC or DMARDs before stroke	No	3/12	No		
Locations of stroke					
Basal ganglion region	13/22 (59.0%)				
Cerebral hemisphere	3/22				
Centrum semiovale	2/22				
Multiple lobes	6/22 (27.0%)				
Probable causes of stroke					
Cervical artery involvement vessels	10/22				
Intracranial vessels arteries	4/22				
Cervical and intracranial	6/22				
And/or HTN	4/22		ICH (2)		
Thrombosis	1/22				
Unknown cause	1/22		SAH (2)		

CRP, C-reactive protein; DMARDs, disease modifying antirheumatic drugs; ESR, erythrocyte sedimentation rate; GC, Glucocorticoid; HTN, Hypertension; ICH, intracerebral hemorrhage; IS, ischemic stroke; SAH, subarachnoid hemorrhage.

Involvement of Intracranial Arteries Associated with Neurological Manifestations

Intracranial artery imaging examination was carried out in 131 out of 411 patients, among which 31 cases had intracranial artery involvement (including 10 patients with stroke and 21 patients without stroke). The pattern of intracranial vascular involvement of the two groups is shown in Table 4. MCA was the most frequently affected intracranial artery, and accounted for 76.9% (10/13) in patients with stroke and 84.3% (27/32) in patients without stroke, respectively; the differences was not statistically significant (P = 0.553). There was no difference in gender and age of disease onset between the two groups. More patients were diagnosed and treated before intracranial vascular involvement was found in patients without stroke, and the difference was statistically significant (P < 0.001).

Treatment and Outcome

Most stroke patients were treated with glucosteroid (GC) and traditional immunosuppressive agents such as cyclophosphamide (CYC), methotrexate (MTX), and azathioprine (AZA), in addition to neurological treatment for stroke. GC was prescribed for 24 of the 26 patients who had stroke. CYC was used in 22 patients and CYC was combined with MTX in 2 patients. AZA was prescribed to 1 patient. Antiplatelet drugs (aspirin or/and clopidogrel) were initiated at the same time when IS occurred. Eight patients were treated with interventional operation procedure: bypass between aorta and

Table 3: Artery involved in patients with stroke

Arteries involved	Total	Stenosis	Occlusion	Dilatation	Subclavian blood steal
Cervical arteries (26/26)					
CCA	19/26 (73%)	2	17	2	
ICA	15/26 (57.7%)	3	12	2	
ECA	1	1			
SCA	19/26 (73%)	6	13	6	2
VA	8	2	6		2
Intracranial arteries (10/26)					
Lt ACA	1		1		
Rt ACA	2	2			
Lt MCA	2		2		
Rt MCA	8	4	4		

ACA, anterior cerebral arteries; CCA, common carotid artery; ECA, external carotid artery; ICA, internal carotid artery; Lt, left; MCA, middle cerebral artery; Rt, right; SCA, subclavian artery; VA, vertebral artery.



Figure 1: Characteristics of Cervical and Intracranial arteries involvement in stroke patients of TA. ACA, anterior cerebral arteries; CCA, common carotid artery; ICA, internal carotid artery; ECA, external carotid artery; MCA, middle cerebral artery; SCA, subclavian artery; VA, vertebral artery.

	Stroke	e (<i>N</i> = 10)	Without st	P value	
Gender (female/male)	:	7/3		7/4	0.495
Age at onset (years)	28.0	28.0 ± 8.3		± 12.3	0.081
Duration (months)	37.0	37.0 ± 27.8		± 66.1	0.065
Numano classification Type V	7	7/10		7/21	0.495
Treatment (GC and DMARDs)	2/10	2/10 (20.0%)		(90.4%)	<0.001
Intracranial arteries	Stenosis	Occlusion	Stenosis	Occlusion	
Lt ACA		1	2		
Rt ACA	2		1		
Lt MCA		2	9	4	0.553
Rt MCA	4	4	11	3	
Lt PCA			1		
Rt PCA			1		

Table 4: Clinical characteristics of intracranial vascular involvement in patients with and without stroke

ACA, anterior cerebral arteries; DMARDs, disease modifying antirheumatic drug; GC, glucosteroid; Lt, left; MCA, middle cerebral Artery; PCA, posterior cerebral arteries; Rt, right.

carotid artery (N = 3); bypass between carotid and subclavian arteries (N = 3); bypass between innominate and carotid arteries and bypass between innominate and subclavian arteries (N = 1); and angioplasty and stenting in aorta (N = 1). One (3.8%) stroke patient died of multiple organ embolism during hospitalization, while the remaining patients improved (Table 5).

Discussion

Prevalence

Stroke is an important and serious complication of TA.^[9] The occurrence of stroke varies from 5% to 17% of the patients in the literature.^[10] In this study, the prevalence of stroke was 6.3%, similar to previous reports. Two systematic reviews showed that the pooled prevalence rate of stroke and TIA in TA patients was 15.8% and 8.9%, respectively.^[11, 12] These differences may be associated with differences in ethnic background.^[13, 14] Approximately 50% of patients manifested with stroke as the initial clinical presentation in this study, while other studies reported even higher rates.^[10, 15] This makes the diagnosis of TA very challenging. Nevertheless, TA should be one of the causes of stroke, particularly in young patients.^[16-18]

Clinical Features and Inflammatory Manifestations

According to the Numano angiographic classification, the most common types of vascular involvement in stroke patients were types V (61.5%) and I (30.8%) in this study, which was also consistent with one previous study in China cohort.^[14, 19] But the Brazilian stroke cohort was constituted more by type I than V.^[10] Our results showed that there was no significant difference in neurological manifestations in stroke patients when compared with non-stroke patients, but patients with stroke had more ophthalmic symptoms, including vision loss. Several

other studies had shown that patients with stroke were more prone to complications with visual impairment than patients without stroke.^[14, 15, 20] The visual symptoms were mainly caused by the occlusion of CCA, resulting in decreased ophthalmic circulation, or "blood steal" of the anterior circulation due to the severe ischemia of the posterior circulation.^[20, 21] This might suggest that severe extracranial artery involvement is the risk factor for stroke.

However, there was no evidence of active inflammation in the majority of patients with stroke, as indicated by the absence of significant increases in acute phase reactants or institutional symptoms such as fever and loss of body weight. This suggested that systemic inflammation was not pre-required for stroke development, but that there was severe shortage of blood supply as reflected by the high frequency of obliteration of the arteries that supply blood to the brain.^[10] This was also consistent with the results of two studies.^[14, 15]

Arteries Involved and MRI Findings

In this study, 22 patients were having IS and 4 patients hemorrhagic stroke. The most commonly involved arteries were CCA and SCA (73%) followed by ICA (57.7%).This was consistent with previous reports that CCA and SCA were the most commonly affected in patients with stroke.^[3, 15, 20] The intracranial artery involvement rate in stroke patients was significantly higher (38.4%) than in non-stroke patients, among which the MCA (76.9%) was the most commonly involved. Other studies also found that the incidence of intracranial vascular involvement in TA patients was high and significantly related to the occurrence of IS.^[14, 15, 22] In this study, we found that cervical artery involvement (10/22) was the most common cause of stroke, followed by dual cervical and intracranial vascular disease (6/22) and intracranial vascular disease

	Drug therapy				Surgery		Improvement rate		
	GC	СҮС	AZA	МТХ	Antiplatelet	Anticoagulation	Bypass surgery	Stent implantation	
IS (N = 22)	20	18	1	2	22	1	7		21/22 (95%)
ICH + SAH (<i>N</i> = 4)	4	4						1	4/4 (100%)

Table 5: Treatment and outcome in patients with and without stroke

AZA, azathioprine; CYC, cyclophosphamide; GC, glucosteroid; ICH, intracerebral hemorrhage; IS, ischemic stroke; MTX, methotrexate; SAH, subarachnoid hemorrhage.

(4/22). In this study, patients with hemorrhagic stroke had a longer course than IS and were associated with hypertension and spontaneous SAH.

Basal ganglia was the most frequent location for infarction, which was consistent with CCA and MCA involvement. Kong *et al.* reported that most of the ischemic lesions were located within the MCA territory or internal/cortical border-zone area.^[15] One recent research from China suggested that the most common site of ischemic infarction was the frontal lobe (19/42, 45.2%), followed by the basal ganglion region (15/42, 35.7%) and parietal lobe (12/42, 28.6%). Multiple cerebral infarction sites were also found in 35 of 42 (83.3%) patients.^[14]

Risk Factors and Prognosis

In 31 patients with intracranial artery involvement, 19.4% patients did not have any neurological manifestations. Therefore, intracranial artery involvement was insidious in general until severe ischemia happened, such as development of TIA or stroke, that also impeded early detection and aggressive treatment before the onset of stroke. Studies on stroke risk factors had shown that hyperlipidemia, higher Indian Takayasu Clinical Activity Score (ITAS) 2010, larger number of involved arteries, and MCA involvement were independent risk factors for cerebral infarction in TA patients.^[14] However, in our study, stroke patients had lower ESR and CRP levels compared to patients without stroke. Further analysis found that patient without stroke after the diagnosis of TA usually had evident inflammation reflected by persistent fever and chest pain that required medical attention when the disease was onset. This might suggest that severe inflammation at disease onset might be a potential protective factor for stroke. Further study is needed to clarify this.

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Author Contributions

All authors made substantial contributions to this work, and all read and approved the final manuscript.

As shown in Table 1, there was no significant difference in the traditional stroke risk factors for stroke between the stroke group and the non-stroke group, which was consistent with the literature reports.^[14, 23] Twenty-five patients in this study improved with GC and traditional immunosuppressive agents, antiplatelet and anticoagulant therapy, or surgery. The in-hospital mortality was not statistically significantly different between the stroke group and the non-stroke group. The reasons for this might be that the cause of stroke was active TA; so, the treatment of TA could improve the outcome in this situation.

Advantages and Limitations

The big enough sample size of this study is a strength to get the prevalence of stroke of this rare disease. The major limitation of this study is that the time span of this study is very big, a lot of progress in the imaging technology and treatment have been made, so the prevalence of stroke may be changed. Another limitation is that the sample size of stroke is relatively small, so the results might be biased.

Conclusion

In conclusion, stroke of TA is rare but should be noted because of the serious sequalae of this disabling condition. Stroke usually occurs in patients with extensive artery involvement, particularly in patients with multifocal artery severe stenosis or occlusion. Intracranial vascular involvement may be a cause of stroke. However, about 50% of stroke cases occur in patients without a history of TA. Aggressive treatment for TA with GC and immunosuppressive agents combined with anti-stroke therapy can improve the prognosis of TA complicated stroke.

Informed Consent

Informed consent was waived because of the retrospective nature of the study.

Ethical Statement

This retrospective study was approved by the Ethics Committees of hospital and was conducted in accordance with the Declaration of Helsinki.

Conflict of Interest

Xiaofeng Zeng is the Editor-in-Chief of the journal, and Xinping Tian is an Executive Editor-in-Chief. The article was subject to the journal's standard procedures, with peer review handled independently of these members and their research groups.

References

[1] Mirouse A, Biard L, Comarmond C, *et al*. Overall Survival and Mortality Risk Factors in Takayasu's Arteritis: A Multicenter Study of 318 Patients. J Autoimmun. 2019;96:35–39.

[2] Park MC, Lee SW, Park YB, *et al.* Clinical Characteristics and Outcomes of Takayasu's Arteritis: Analysis of 108 Patients Using Standardized Criteria for Diagnosis, Activity Assessment, and Angiographic Classification. Scand J Rheumatol. 2005;34: 284–292.

[3] Lirui Y, Huimin Z, Xiongjing J, *et al.* Clinical Features and Outcomes of Takayasu Arteritis with Neurological Symptoms in China: A Retrospective Study. J Rheumatol. 2015;42:1846–1856.

[4] Zhou L, Ni J, Gao S, *et al*. Neurological Manifestations of Takayasu Arteritis. Chin Med Sci J. 2011;26:227–230.

[5] Ringleb PA, Strittmatter EI, Hartmann M, *et al.* Cerebrovascular Manifestations of Takayasu Arteritis in Europe. Rheumatology. 2005;44:1012–1015.

[6] Hata A, Noda M, Moriwaki R, *et al.* Angiographic Findings of Takayasu Arteritis: New Classification. Int J Cardiol. 1996;54:S155–S163.

[7] Sacco RL, Kasner SE, Broderick JP, *et al.* An Updated Definition of Stroke for the 21st Century: A Statement for Healthcare Professionals from the American Heart Association/American Stroke Association. Stroke. 2013;44:2064–2089.

[8] Easton JD, Saver JL, Albers GW, *et al.* Definition and Evaluation of Transient Ischemic Attack: A Scientific Statement for Healthcare Professionals from the American Heart Association/American Stroke Association Stroke Council; Council on Cardiovascular Surgery and Anesthesia; Council on Cardiovascular Radiology and Intervention; Council on Cardiovascular Nursing; and the Interdisciplinary Council on Peripheral Vascular Disease. The American Academy of Neurology Affirms the Value of this Statement as an Educational Tool for Neurologists. Stroke. 2009;40:2276–2293.

[9] Priscille C, Thibaud C, Charlotte R, *et al.* Cerebrovascular Events in Takayasu Arteritis: A Multicenter Case-Controlled Study. J Neurol. 2018;265:757–763.

[10] de Paula LE, Alverne AR, Shinjo SK. Clinical and Vascular Features of Takayasu Arteritis at the Time of Ischemic Stroke. Acta Reumatologica Portuguesa. 2013;38:248–251. [11] Duarte MM, Geraldes R, Sousa R, *et al.* Stroke and Transient Ischemic Attack in Takayasu's Arteritis: A Systematic Review and Meta-analysis. J Stroke Cerebrovasc Dis. 2016;25:781–791.

[12] Kim H, Barra L. Ischemic Complications in Takayasu's Arteritis: A Meta-Analysis. Semin Arthritis Rheum. 2018;47:900–906.

[13] Laurent A, Julien H, Nicolas L, *et al.* Takayasu Arteritis in France: A Single-Center Retrospective Study of 82 Cases Comparing White, North African, and Black Patients. Medicine. 2010;89:1–17.

[14] Kong F, Huang X, Su L, *et al.* Risk Factors for Cerebral Infarction in Takayasu Arteritis: A Single-Centre Case-Controlled Study. Rheumatology (Oxford). 2021;61:281–290.

[15] Hwang J, Kim SJ, Bang OY, *et al.* Ischemic Stroke in Takayasu's Arteritis: Lesion Patterns and Possible Mechanisms. J Clin Neurol. 2012;8:109–115.

[16] Cheo SW, Zamin HM, Low QJ, *et al*. A Case of Takayasu Arteritis Presenting with Young Stroke. Med J Malaysia. 2020;75:745–747.

[17] Gouda W, Alsaqabi F, Alkadi A, *et al.* Ischemic Stroke as the First Presentation of Takayasu's Arteritis in Young Male. Clinical Case Reports. 2020;8:258–261.

[18] Pereira VC, de Freitas CCM, Luvizutto GJ, *et al.* Stroke as the First Clinical Manifestation of Takayasu's Arteritis. Case Rep Neurol. 2014;6:271–274.

[19] Bicakcigil M, Aksu K, Kamali S, *et al.* Takayasu's Arteritis in Turkey – Clinical and Angiographic Features of 248 Patients. Clin Exp Rheumatol. 2009;27:S59–S64.

[20] Kim HJ, Suh DC, Kim JK, *et al.* Correlation of Neurological Manifestations of Takayasu's Arteritis with Cerebral Angiographic Findings. Clin Imaging. 2005;29:79–85.

[21] Gao P, Dmytriw AA, Wang T, et al. Contemporary Challenges of Acute Ischemic Stroke in Takayasu Arteritis. Stroke. 2020;51:e280– e284.

[22] Bond KM, Nasr D, Lehman V, *et al.* Intracranial and Extracranial Neurovascular Manifestations of Takayasu Arteritis. AJNR Am J Neuroradiol. 2017;38:766–772.

[23] Soto ME, Espinola N, Flores-Suarez LF, *et al.* Takayasu Arteritis: Clinical Features in 110 Mexican Mestizo Patients and Cardiovascular Impact on Survival and Prognosis. Clin Exp Rheumatol. 2008;26:S9–S15.