ORIGINAL ARTICLE
J Clin Neurol 2012;8:109-115

Print ISSN 1738-6586 / On-line ISSN 2005-5013
http://dx.doi.org/10.3988/jcn.2012.8.2.109

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Ischemic Stroke in Takayasu's Arteritis: Lesion Patterns and Possible Mechanisms

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Received July 12, 2011
Revised September 14, 2011
Accepted September 14, 2011

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Background and Purpose The purpose of the present study was to use brain magnetic resonance imaging (MRI) and magnetic resonance angiography (MRA) to identify the mechanism of stroke in patients with Takayasu's arteritis (TA).

Methods Among a retrospective cohort of 190 TA patients, 21 (3 males and 18 females) with a mean age of 39.9 years (range 15-68 years) who had acute cerebral infarctions were included in lesion pattern analyses. The patients' characteristics were reviewed, and infarction patterns and the degree of cerebral artery stenosis were evaluated. Ischemic lesions were categorized into five subgroups: cortical border-zone, internal border-zone, large lobar, large deep, and small subcortical infarctions.

Results In total, 21 ischemic stroke events with relevant ischemic lesions on MRI were observed. The frequencies of the lesion types were as follows: large lobar (*n*=7, 33.3%), cortical border zone (*n*=6, 28.6%), internal border zone (*n*=1, 4.8%), small cortical (*n*=0, 0%), and large deep (*n*=7, 33.3%). MRA revealed that 11 patients had intracranial artery stenosis.

Conclusions Hemodynamic compromise in large-artery stenosis and thromboembolic mechanisms play significant roles in ischemic stroke associated with TA.

J Clin Neurol 2012;8:109-115

Key Words vasculitis, thromboembolism, intracranial artery stenosis.

Introduction

Takayasu's arteritis (TA) is a chronic inflammatory disease of unknown etiology that primarily affects the aorta and its main branches.[1] Vascular inflammation has been shown to cause arterial stenosis, occlusion, dilatation, and aneurysms. Clinical features such as claudication, renal hypertension, congestive heart failure, and coronary artery disease usually reflect limb or organ ischemia resulting from gradual stenosis of the involved arteries. Neurological manifestations that may accompany TA include headache, dizziness, visual disturbance or loss of vision, transient ischemic attacks (TIAs), and stroke.[2] It has been reported that 10-20% of patients with TA will have an ischemic stroke or a TIA.[3,4] Although cerebral ischemic attacks are not common complications of TA, they can give rise to devastating neurological symptoms and be a major cause of morbid events and premature death.[5] Antiplatelet agents and anticoagulants have been used for the prevention of stroke. In some cases surgical treatments including bypass surgery or stent insertion have also been advocated.[6,7] However, investigations into the mechanism of ischemic stroke in TA remain inadequate.[1]

Previous studies have indicated that the lesion patterns seen on magnetic resonance imaging (MRI) and magnetic resonance angiography (MRA) suggest particular stroke mechanisms.[8,9] In the current study we determined some of the topographical characteristics of ischemic stroke in patients with TA in order to improve our understanding of the possible underlying mechanisms.

Methods

Patients

We performed a retrospective analysis of 207 patients diagnosed with TA at the Samsung Medical Center between January 1993 and July 2009. TA patients were identified by reviewing the registry in which data had been prospectively collected. The local institutional review board approved this study. The diagnosis of TA was assessed according to the American College of Rheumatology Criteria for the Classification of TA, which is based on the presence of symptoms and signs of ischemic, inflammatory large-vessel disease, as well as supportive serological information and arteriographic findings.[10] The characteristics and stroke risk factors of the patients were reviewed through previous medical records. Lesion patterns and the degree of stenosis in both the intracranial and extracranial arteries were evaluated through diffusion-weighted MRI (DWI), fluid-attenuated inversion recovery (FLAIR) MRI, and MRA.

We compared the age, gender, TA-related inflammatory markers, and other cerebrovascular risk factors such as hypertension, diabetes mellitus, dyslipidemia, ischemic heart disease, history of smoking, renal dysfunction, and prior transient monocular blindness (TMB) between stroke TA patients and nonstroke TA patients. The history of previous hemispheric TIA was not considered because it is difficult to distinguish from extremity claudication caused by peripheral ischemia.

We included patients who had been confirmed with ischemic stroke in stroke lesion pattern analysis. Stroke was defined as focal cerebral dysfunction relevant to an ischemic lesion on MRI. We excluded patients who 1) did not have a stroke event, 2) had TIA or TMB without ischemic lesions on MRI, 3) had hemorrhagic stroke, 4) had been referred and whose MRI and MRA were not available to us, or 5) who had potential sources of cardioembolisms such as atrial fibrillation, mitral stenosis, a prosthetic valve, dilated cardiomyopathy, sick sinus syndrome, acute bacterial endocarditis, or patent foramen ovale.

Among the 207 TA patients (183 females) who were originally surveyed, we ultimately included 190 patients (170 females) in our study. We excluded four referral patients whose MRI and MRA were not available to us, three patients who had hemorrhagic stroke, and ten patients who had potential cardioembolic sources.

MRI and MRA

Ischemic brain lesions were assessed and defined as hyperintense signal alterations on DWI or FLAIR MRI. We then classified the distribution patterns of stroke lesions on MRI as well as the clinical manifestations. All ischemic lesions were categorized into the following five subgroups according to lesion size and topographical distribution based on published templates:[11,12]

1. Cortical border-zone infarction: ischemic lesions mainly involving the border between the two main cerebral arteries, the border-zone area between the middle cerebral artery (MCA) and the anterior cerebral artery, or the posterior cerebral artery.

2. Internal border-zone infarction: hyperintense lesions at the border of the deep and superficial perforating arterial territories of the MCA.

3. Large lobar infarction: cortical infarction involving one or more divisions of a large vessel with or without subcortical lesions.

4. Large deep subcortical infarction: single large striatocapsular lesions greater than 2 cm in diameter.

5. Small subcortical infarction: small single ischemic lesions less than 2 cm in diameter in the subcortical area suggesting lacunae.

A three-dimensional time-of-flight MRA scan of the intracranial arteries and gadolinium-enhanced MRA of the extracranial arteries was obtained from all patients. The standard Warfarin Versus Aspirin for Symptomatic Intracranial Disease Trial method was used to measure the degree of stenosis.[13] The degree of arterial stenosis on MRA was graded as mild (<50%), moderate (50-69%), or severe (70-100%) according to the reduction in the diameter of the narrowest vessels. For intracranial artery stenosis (ICAS), the lumen reduction of the vertebrobasilar artery assessed on both the targeted maximal-intensity projection MRA and the source images to reduce the possibility of overestimation of stenosis inherent in the time-of-flight MRA technique. Two experienced observers who were blinded to the clinical data analyzed the images, and discrepancies were resolved through consensus.

Statistical analyses

Continuous data are presented as means and standard deviations, while categorical variables are presented as absolute and relative frequencies. We analyzed the differences between stroke and nonstroke patients using the chi-square test or Fisher's exact test for categorical variables and Student's *t*-test or the Mann-Whitney *U*-test for continuous variables. A probability value of $p<0.05$ was considered to be indicative of statistical significance. All statistical analyses were performed using commercially available software (SPSS for Windows, version 15.0; SPSS, Chicago, IL, USA).

Results

Of the 190 TA patients included in this study, 21 stroke patients (18 females) with a mean age of 39.9 years (range 15-68 years) were identified.

Table 1. Stroke risk factor profiles of the stroke and nonstroke Takayasu's arteritis (TA) groups

	Stroke group (*n*=21)	Nonstroke group (*n*=169)	*p*
Age at TA diagnosis (years), mean (range)	39.9 (15-68)	39.5 (7-68)	0.736
Male gender, *n* (%)	3 (14.3)	17 (10.1)	0.385
Conventional stroke risk factors			
Hypertension, *n* (%)	14 (66.7)	114 (67.5)	0.560
Diabetes mellitus, *n* (%)	4 (19.0)	9 (5.3)	0.059
Dyslipidemia, *n* (%)	6 (28.6)	38 (22.4)	0.584
Ischemic heart disease, *n* (%)	2 (9.5)	34 (20.1)	0.195
Smoke, *n* (%)	3 (14.3)	18(10.7)	0.418
TA-related risk factors			
TMB, *n* (%)	8 (38.1)	19 (11.2)	0.003‡
Elevated ESR*, *n* (%)	12 (57.1)	95 (56.2)	0.563
Elevated CRP†, *n* (%)	8 (38.1)	52 (30.8)	0.326
Renal failure, *n* (%)	0 (0)	7 (4.1)	0.303

*ESR>27 mm/hour, †CRP>0.3 mg/dL, ‡p<0.05.
TMB: transient monocular blindness, ESR: erythrocyte sedimentation rate, CRP: C-reactive protein.

Conventional stroke risk factors and other TA risk factors

Conventional stroke risk factor profiles did not differ significantly between the stroke and nonstroke TA groups. Stroke and nonstroke patients had similar prevalence rates of hypertension, diabetes mellitus, dyslipidemia, and history of smoking (Table 1). There were also no differences when comparing TA-related factors such as erythrocyte sedimentation rate, C-reactive protein, and chronic renal failure. The frequency of previous TMB history was significantly higher in the stroke group.

MRI findings

In total, 21 first-ever ischemic stroke events with relevant ischemic lesions on MRI were observed. Nine and 12 stroke events were identified by DWI and FLAIR imaging, respectively. Most of the ischemic lesions were located within the MCA territory or internal/cortical border-zone area. Stroke patterns and angiographic features as well as clinical information for all patients are provided in Table 2. The frequencies of the lesion types were as follows (Fig. 1): large lobar, *n*=7 (33.3%); cortical border zone, *n*=6 (28.6%); internal border zone, *n*=1 (4.8%); and large deep, *n*=7 (33.3%). There were no small subcortical infarctions in patients with TA.

MRA findings

As predicted, extracranial carotid artery stenosis or subclavian artery stenosis relevant to lesions were found in most ischemic stroke patients (71.4%; Table 2). Furthermore, MRA revealed that 11 patients had ICAS including the intracranial internal carotid artery, distal basilar artery, MCA, anterior cerebral artery, and posterior cerebral artery. Fig. 2 shows all ICAS data related to the TA patients. ICAS relevant to stroke lesions were found in 9 of 11 cases (81.8%); the degree of ICAS was mild in 4 (36.4%), moderate in 3 (27.3%), and severe in 4 (36.4%). The frequency of ICAS relevant to stroke was lower in the cortical border-zone infarctions (0%) than in large lobar (57.1%), internal border-zone (100%), and large deep (57.1%) infarctions (Table 3).

We examined the steno-occlusive state of the feeding artery in our nine patients with ICAS relevant to ischemic lesions separately according to stroke subdivision, and from this inferred the effect of ICAS in the stroke mechanism. ICAS was relatively common (57.1%) in large lobar infarction patterns, but every case exhibited an ipsilateral carotid artery steno-occlusive lesion. Conversely, ICAS lesions were not seen in six cortical border-zone infarction cases. Of the seven large deep patterns, four cases exhibited a relevant ICAS, but one was combined with carotid occlusion. The prevalence of ICAS relevant to ischemic lesions was higher in the large deep group (57.1%) when the cases of superimposed steno-occlusive extracranial feeding arteries were excluded.

Discussion

We found that 11.1% of the TA patients in this study experienced stroke events, which is consistent with previous prospective studies.[4] Stroke is an uncommon symptom for most TA patients and is rarely reported as the first manifestation; however, Sikaroodi et al.[14] reported one case of stroke as the first manifestation of TA. In our study, 52.3% of stroke patients were first diagnosed with TA upon admission for an initial stroke event. It is recommended that if suspected, young stroke patients should be examined for TA based on nonspecific systemic symptoms such as fever, malaise, dizziness, and arm claudication.

Table 2. Summary of clinical and imaging features of infarctions

Case	Subgroup	Sex/Age (years)	Main symptom	Lesion site	MRI	ICAS		Carotid artery stenosis		Stroke risk factors		
						Site	Degree	Site	Degree	HTN	DM	Lipid
1	Large lobar	F/25	Hemiparesis	Rt MCA	DWI	Rt M1 Rt A1	Occlusion Severe	Rt CCA Lt CCA	Occlusion Moderate	N	N	N
2	Large lobar	M/47	Hemiparesis	Rt MCA	FLAIR	N	N	Rt CCA	Moderate	N	N	Y
3	Large lobar	F/39	Hemiparesis Aphasia	Lt MCA	FLAIR	Lt M2	Mild	Lt CCA	Severe	N	N	N
4	Large lobar	F/24	Hemiparesis	Rt MCA	DWI	Rt M1	Moderate	Rt CCA Lt CCA	Occlusion Occlusion	Y	N	N
5	Large lobar	F/34	Hemiparesis Hemianopsia	Rt MCA	FLAIR	N	N	Rt SCA	Occlusion	N	N	Y
6	Large lobar	F/33	Hemiparesis	Rt MCA	FLAIR	Rt M1	Mild	Rt CCA Lt SCA	Moderate Occlusion	N	N	N
7	Large lobar	F/15	Hemiparesis Aphasia	Lt MCA	DWI	N	N	Lt CCA	Occlusion	N	N	N
8	CBDZ	F/15	Hemiparesis	Lt BDZ	DWI	N	N	Rt CCA Lt CCA	Occlusion Occlusion	Y	N	Y
9	CBDZ	F/45	Hemiparesis	Rt BDZ	DWI	N	N	Rt CCA Lt CCA	Severe Severe	Y	Y	Y
10	CBDZ	F/46	Hemiparesis	Lt BDZ	FLAIR	N	N	Rt CCA Lt CCA	Moderate Severe	Y	N	N
11	CBDZ	F/17	Hemiparesis	Rt BDZ	FLAIR	Lt dICA	Moderate	Rt CCA Lt CCA	Occlusion Occlusion	N	N	N
12	CBDZ	M/34	Hemiparesis	Rt BDZ	FLAIR	N	N	Rt SCA Lt CCA	Mild Occlusion	Y	N	N
13	CBDZ	F/49	Hypesthesia	Bo BDZ	DWI	N	N	Lt SCA	Severe	Y	Y	Y
14	IBDZ	F/49	Hemiparesis	Rt BDZ	DWI	Rt M2	Mild	N	N	Y	N	Y
15	Large deep	F/51	General Weakness	Rt SC	FLAIR	Rt M1 Lt M1	Occlusion Severe	N	N	Y	N	N
16	Large deep	F/33	Hemiparesis	Lt SC	DWI	N	N	Rt CCA	Mild	Y	N	Y
17	Large deep	F/38	Hemiparesis	Rt SC	FLAIR	Rt P2	Mild	Rt CCA	Moderate	Y	Y	N
18	Large deep	F/43	Hemiparesis	Rt SC	DWI	Rt M1	Severe	N	N	Y	N	Y
19	Large deep	M/43	Hemiparesis	Rt SC	FLAIR	N	N	Rt CCA Lt CCA	Occlusion Moderate	Y	N	Y
20	Large deep	F/37	Hemiparesis	Lt SC	FLAIR	Lt M1	Moderate	Rt CCA Lt CCA	Severe Occlusion	Y	N	N
21	Large deep	F/46	Hemiparesis	Rt SC	FLAIR	Bo M1,2 Rt A1,2	Severe Mild	Lt CCA Lt ICA	Moderate Severe	Y	Y	Y

BDZ: border zone, Bo: both, CBDZ: cortical border zone, CCA: common carotid artery, dICA: distal internal carotid artery, DM: diabetes mellitus, DWI: diffusion-weighted imaging, F: female, FLAIR: fluid-attenuated inversion recovery, HTN: hypertension, IBDZ: internal border zone, ICA: internal carotid artery, ICAS: intracranial artery stenosis, Lt: left, M: male, MCA: middle cerebral artery, MRI: magnetic resonance imaging, N: no, Rt: right, SC: striatocapsular, SCA: subclavian artery, Y: yes.

The mean age of diagnosis for TA was in the third decade, and did not significantly differ between the stroke and nonstroke TA groups. The mean time from TA diagnosis to stroke onset was 1.6 years (range 0-4 years). Strokes developed in TA patients at much a younger age than observed for strokes related to atherosclerotic mechanisms. The prevalence of conventional stroke risk factors, except for hypertension and dyslipidemia, was lower among the TA patients than for traditional atherosclerotic stroke. The relatively high prevalence of hypertension is probably due to the involvement of renal artery stenosis.[4,15] Therefore, stroke in TA patients seems to develop via a different mechanism than conventional atherosclerotic changes. The TA-related serologic markers erythrocyte sedimentation rate and C-reactive protein, which represent disease activity, also did not differ significantly between the stroke and nonstroke groups. However, the time intervals from stroke onset to laboratory studies were inconsistent and relatively long. Therefore, a homogeneous large study of acute stroke in TA patients is needed to establish a correlation between TA disease activity and ischemic stroke.

Known predispositions to stroke in TA patients were previously limited to TMB history. Also known as amaurosis fugax, TMBs are TIAs involving the anterior cerebral circulation and are caused by thromboembolisms or hypoperfusion. Previous

studies have suggested that TMB history is a warning sign for stroke.[16,17] Our data indicated that previous TMB may also be related to future ischemic stroke in TA patients.

MRI analysis revealed that most of the ischemic lesions were located at MCA branches or in the internal/cortical border-zone area. Large lobar type and cortical border-zone infarctions were documented in 33.3% and 28.6% of cases, respectively. Wedge-shaped large lobar and cortical border-zone infarctions are related to embolic mechanisms.[18] In comparison, internal border-zone infarctions - which are known to occur via a hemodynamic compromise mechanism[19] - accounted for only 4.8% of all the stroke events. These results highlight not only the hemodynamic compromise in large-artery stenosis but also the thromboembolic mechanism in ischemic stroke of TA. There were no cases of a small subcortical infarction suggesting a lacunar infarction among our TA patients.

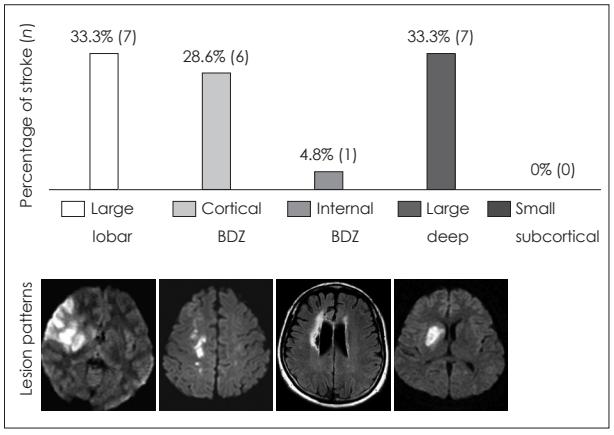

Fig. 1. Comparison of stroke patterns in Takayasu's arteritis. BDZ: border zone infarction.

As noted above, most TA patients are young and rarely have conventional atherosclerotic risk factors. With respect to atherosclerotic carotid stenosis, embolic cerebral infarction is usually attributed to plaque rupture or thrombotically active carotid plaques associated with high inflammatory infiltrates.[20,21] Some studies have revealed premature atherosclerosis in TA patients based on ultrasonography or autopsy results.[22-24] In particular, Seyahi et al.[15] reported that 27% of TA patients possessed atherosclerotic plaques.[23] From this, we can surmise that a similar mechanism may be involved in creating thromboembolisms, such as ruptures of atheromatous plaques or artery-to-artery embolisms.

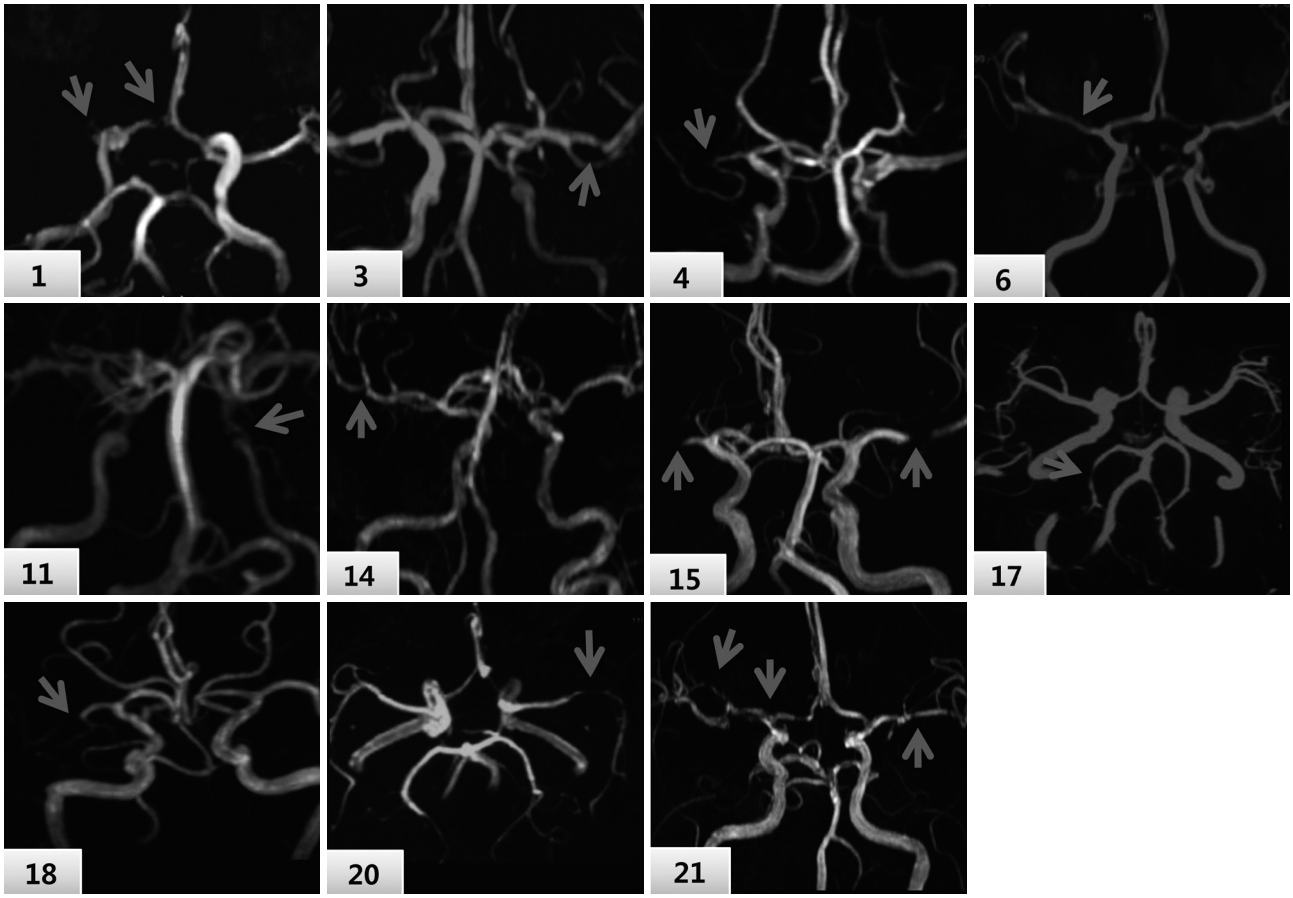

Fig. 2. Magnetic resonance angiography findings of intracranial artery stenosis in patients with Takayasu's arteritis. Arrows indicate the site of intracranial artery stenosis.

Table 3. Relationships between ischemic patterns and relevant arterial stenosis

Lesion pattern	Total number	Ipsilateral ICAS, *n* (%)	Ipsilateral ECAS, *n* (%)
Large lobar	7	4 (57.1)	7 (100)
Cortical BDZ	6	0 (0)	5 (83.3)
Internal BDZ	1	1 (100)	0 (0)
Large deep subcortical	7	4 (57.1)	4 (57.1)
Small subcortical	0	0	0

BDZ: border zone, ICAS: intracranial artery stenosis, ECAS: extracranial artery stenosis.

Most previous reports have described TA as medium- or large-vessel arteritis involving the aorta and its main branches.[1,4] To the best of our knowledge, only three case reports have described ICAS in TA, as discovered at autopsy or through arteriographic findings. Klos et al.[26] described two patients with TA who had ischemic stroke due to intracranial involvement, in whom the cause of the infarction was proposed to be vasculitis.[25] In our study revealed that more than half of the TA patients with stroke had ICAS. Based on our results, we believe that intracranial involvement in TA may be under-recognized, and that cerebral angiography should be considered for patients diagnosed with TA. Given that TA patients are young and relatively free from atherosclerotic risk factors except hypertension and dyslipidemia, vascular inflammation may be an important risk factor in ICAS.[22]

From our analysis of the stroke subgroup distribution, ICAS seems to be more likely when patients have large deep subcortical infarctions and internal border-zone infarctions than other types of infarction. A recent study regarding lesion patterns in cases of concurrent atherosclerosis of ICAS revealed a high prevalence of perforating artery infarctions and border-zone infarctions in the ischemic lesion distribution.[27] Previous studies have suggested that ICAS is related not only to artery-to-artery embolisms but also to hemodynamic compromise.[18,28-31] Further studies with large case series are needed to confirm whether ICAS in TA patients is related to a diverse pattern of ischemic stroke.

This study was subject to several limitations. First, since many of the patients were referred to our hospital some time after their stroke events occurred, laboratory and image data were not homogeneous. Some patients were diagnosed by FLAIR imaging because no DWI images were available. Although FLAIR imaging is less sensitive than DWI, we were still able to diagnose and locate stroke lesions accurately using clinical correlations. Second, only a small number of stroke patients were included in order to analyze stroke risk factors and ICAS between lesion subtypes. The low prevalence of stroke in TA made it impossible to include a large number of stroke patients in our analysis; however, this study currently represents the largest clinical series regarding stroke in TA patients. Third, the prevalence of ICAS in TA patients with stroke was higher than in previous studies. Some partial reanalyzed steno-occlusive arterial states produced by a proximal arterial embolic source were thought to have contributed to the high prevalence of ICAS. Moreover, the measurable degree of stenosis may vary between MRA and conventional angiograms. Although we analyzed the source images to reduce the possibility of overestimation of stenosis, MRA may overestimate the degree of ICAS. Directly comparing the ICAS prevalence between our study and previous studies is impossible due to different criteria being used for patient selection. We classified the lesion pattern as identified on DWI or FLAIR images; however, the chronic large-artery steno-occlusive state may alter the collateral flow and cerebral artery territory, which may limit the ability to establish the stroke mechanism in TA patients using lesion pattern analysis alone. Future investigations with perfusion images and conventional angiography would be helpful in determining the stroke mechanism. The final limitation of this study is the lack of pathologic proof of vasculitis. However, considering that the American College of Rheumatology Criteria for the Classification of TA yielded a sensitivity and specificity of more than 90%, there is little likelihood of overdiagnosis of TA in patients with conventional risk factors for stroke.[10]

The factor that was most associated with stroke in TA patients was previous TMB history. The finding that large lobar, cortical border-zone, and large deep infarctions were common stroke types suggests that a thromboembolic mechanism underlies stroke in TA. Furthermore, ICAS may be more prevalent in TA than was previously thought, which suggests that intracranial involvement is relatively common in TA. Future studies involving large numbers of subjects and focusing on the precise pathophysiological mechanisms leading to stenosis would help our understanding of its relationship with ischemic stroke in TA patients.

Conflicts of Interest

The authors have no financial conflicts of interest.

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