ORIGINAL RESEARCH

The Etiology of Intracranial Artery Stenosis in Autoimmune Rheumatic Diseases——An Observational High-Resolution Magnetic Resonance Imaging Study

Shun Li, Qiuyu Yu, Yangzhong Zhou, Manqiu Ding, Huanyu Zhou, Yiyang Liu, Yinxi Zou, Haoyao Guo, Yuelun Zhang, Mengtao Li, Mingli Li, Yan Xu, Weihai Xu *.

ABSTRACT

BACKGROUND AND PURPOSE: Autoimmune rheumatic diseases (AIRD) can cause intracranial artery stenosis (ICAS) and lead to stroke. This study aimed to characterize patients with ICAS associated with AIRD.

MATERIALS AND METHODS: Utilizing data from a high-resolution magnetic resonance imaging (HRMRI) database, we retrospectively reviewed AIRD patients with ICAS. Stratification into vasculitis, atherosclerosis, and mixed athero-vasculitis subtypes was based on imaging findings, followed by a comparative analysis of clinical characteristics and outcomes across these subgroups.

RESULTS: Among 139 patients (45.1±17.3 years; 64.7% females), 56 (40.3%) were identified with vasculitis, 57 (41.0%) with atherosclerosis, and 26 (18.7%) with mixed athero-vasculitis. The average interval from AIRD-onset to HRMRI was 5 years. Patients with vasculitis presented with a younger age of AIRD-onset (34.5±19.4 years), nearly ten years earlier than other groups (P=0.010), with a higher artery occlusion incidence (44.6% vs. 21.1% and 26.9%, P=0.021). Patients with atherosclerosis showed the highest cardiovascular risk factor prevalence (73.7% vs. 48.2% and 61.5%, P=0.021) but lower intracranial artery wall enhancement instances (63.2% vs. 100% in others, P<0.001). The mixed athero-vasculitis group, predominantly male (69.2% vs. 30.4% and 25.6%, P<0.001), exhibited the most arterial involvement (5 arteries per person vs. 3 and 2, P=0.001). Over an average 21-month follow-up, 23 (17.0%) patients experienced stroke events, and 8 (5.9%) died, with the mixed athero-vasculitis group facing the highest risk of stroke events (32.0%) and the highest mortality (12.0%).

CONCLUSIONS: Intracranial arteries are injured and lead to heterogeneous disease courses when exposed to AIRD and cardiovascular risk factors. While atherosclerosis acceleration is common, vasculitis may further contribute to early-developed occlusion and multiple artery involvement. Varied intracranial arteriopathies may result in different outcomes.

ABBREVIATIONS: ICAS = intracranial artery stenosis; AIRD = Autoimmune rheumatic diseases; HRMRI = high-resolution magnetic resonance imaging.

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From the Department of Neurology (Shun Li, Qiuyu Yu, Manqiu Ding, Huanyu Zhou, Yiyang Liu, Yinxi Zou, Haoyao Guo, Yan Xu, Weihai Xu), State Key Laboratory of Complex Severe and Rare Diseases, Peking Union Medical College Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College, Beijing, China; Department of Rheumatology and Clinical Immunology (Yangzhong Zhou, Mengtao Li), Peking Union Medical College Hospital, Chinese Academy of Medical Sciences & Peking Union Medical College, Beijing, China; Center for Prevention and Early Intervention (Yuelun Zhang), National Infrastructures for Translational Medicine, Institute of Clinical Medicine, Peking Union Medical College Hospital, Chinese Academy of Medical Science and Peking Union Medical College, Beijing, China; Department of Radiology (Mingli Li), Peking Union Medical College Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College, Beijing, China

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Please address correspondence to Weihai Xu, MD, Department of Neurology, State Key Laboratory of Complex Severe and Rare Diseases, Peking Union Medical College Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College, Shuaifuyuan1, Dongcheng District, Beijing 100730, China; e-mail: xuwhpumch @qq.com.

SUMMARY SECTION

PREVIOUS LITERATURE: Autoimmune rheumatic diseases (AIRD) can cause intracranial artery stenosis (ICAS) and lead to stroke, yet the etiology of this ICAS has not been systematically reported in the previous literature.

KEY FINDINGS: A novel subtype characterized by the coexistence of atherosclerosis and vasculitis was identified and named mixed athero-vasculitis, which not only encompasses the characteristics of both arteriosclerosis (older) and vasculitis (more intracranial artery wall enhancement), but also presents unique features (male dominance, multiple arterial involvement), potentially resulting in the worst outcomes.

KNOWLEDGE ADVANCEMENT: The results emphasize that intracranial arteries are injured and lead to heterogeneous disease courses when exposed to AIRD and cardiovascular risk factors. While atherosclerosis acceleration is common, vasculitis may further contribute to early-developed occlusion and multiple artery involvement.

INTRODUCTION

Autoimmune rheumatic diseases (AIRD) are characterized as immune dysregulation, primarily affecting joints and muscles, and causing damage to host tissue and organs.[1] This category encompasses diseases including systemic vasculitis, systemic lupus erythematosus, primary antiphospholipid syndrome, rheumatoid arthritis and Sjogren's syndrome, etc.[1] AIRD are known to increase the risk of cardiovascular and cerebrovascular events, particularly among young individuals.[2] The underlying mechanism is primarily attributed to the arterial diseases, which is among the most common complications of AIRD.[3, 4] Previous studies have indicated that AIRD accelerate the risk of premature coronary artery diseases and carotid artery diseases, mostly premature atherosclerosis or vasculitis.[3, 4] Intracranial artery stenosis (ICAS) may also occur in AIRD patients at a young age.[5, 6] However, the underlying pathophysiology remains insufficiently studied, in part due to the difficulties in establishing an etiological diagnosis through conventional lumen imaging. Whether it involves intracranial vasculitis or atherosclerosis, ICAS may manifest as segmental artery narrowing and post-stenotic dilatation on MRA, CTA or DSA.[7] The uncertain etiology significantly complicates clinical decision-making and lead to confused treatment.

In the last decade, high-resolution magnetic resonance imaging (HRMRI) has emerged as a non-invasive technique for visualizing intracranial artery wall structure.[8] Previous studies have suggested that HRMRI is instrumental in identifying intracranial artery diseases, including atherosclerosis, dissection, moyamoya disease, vasculitis and reversible cerebral vasoconstriction syndrome.[9] In this study, our objectives were to elucidate intracranial artery diseases associated with AIRD patients using HRMRI, and compare the difference of the clinical characteristics and outcomes across the etiology subgroups. This article follows the STROBE guidelines.

MATERIALS AND METHODS

This is a retrospective analysis of data from the HRMRI database spanning January 2015 to September 2023 at Peking Union Medical College Hospital. Ethical approval for this study was granted by the local ethics committee (K24C1320).

Patients' Selection

Patients were included if they: 1) had ICAS on MRA (including C6/C7 segment of ICA, M1/M2 segment of MCA, A1 segment of anterior cerebral artery, V4 segment of vertebral artery, basilar artery, and P1 segment of posterior cerebral artery); 2) had a diagnosis of AIRD, confirmed by experienced rheumatologists according to American College of Rheumatology/European League Against Rheumatism classification criteria.[10-15] Patients with poor image quality were excluded. Exclusion criteria also encompassed patients diagnosed with primary central nervous system vasculitis, moyamoya disease, and reversible cerebral vasoconstriction syndrome, which were attributed to the high heterogeneity of etiology besides AIRD.[7, 16, 17]

Imaging Protocol

All MRI scans were performed on two 3.0 T systems (CUBE on GE, and SPACE on Siemens), following the standardized protocol.[18, 19] The protocol included conventional 3-dimensional TOF MRA, DWI, ADC, 3-dimensional T1-weighted head-neck joint HRMRI, and 2-dimensional T2-weighted vessel wall imaging of the MCA. Contrast enhancement was applied selectively to 3-dimensional T1WI (CUBE system) following Gadolinium administration (0.01mmol/Kg Gadopentetate dimeglumine). The imaging parameters are listed in the **Online Supplemental Table 1**.

Imaging Definition

Image analysis was performed on each stenotic artery and individuals were categorized into three subtypes (**Fig 1**): 1) atherosclerosis, characterized by eccentric vessel wall thickening in the orthogonal plane, with the maximal wall thickness exceeding twice the thinnest wall thickness upon visual inspection;[18] 2) vasculitis, characterized by concentric stenosis in the orthogonal plane, potentially accompanied by concentric enhancement following Gadolinium administration;[20] 3) mixed athero-vasculitis, representing the coexistence of atherosclerosis and vasculitis within a single patient, manifested across different arteries or within distinct segments of a single artery. Concentric enhancement was interpreted as circular when uniform or circumferential thickening occurred, whereas eccentric enhancement was identified in the absence of 360° circumferential thickening or when the thickest portion exceed twice the thinnest wall thickness in cases showing circumferential enhancement.[21] The degree of artery stenosis was evaluated according to the WASID (Warfarin-Aspirin Symptomatic Intracranial Disease) criteria.[22] Upon completion of vascular imaging follow-up, the imaging data were re-examined to ascertain changes in the stenotic artery etiology and the degree of stenosis.[23] All images were independently evaluated using the Osirix software (Version 14.0.1) by two readers (L. S and L. ML, with 8 and 20 years of experience, respectively). Should a disagreement arise, a third reader (X. WH, with 20 years of experience) was consulted to make a final decision.

Clinical Characteristics and Outcomes

Clinical characteristics, including age at HRMRI examination, AIRD-onset age, stroke-onset age, gender, and traditional cardiovascular risk factors (hypertension, hyperlipidemia, diabetes, and smoking) were collected. Given the delayed diagnosis of AIRD, the age of the earliest symptoms associated with AIRD was defined as the AIRD-onset age.[1] If stroke was the initial manifestation of AIRD, especially in patients with primary antiphospholipid syndrome, the age at stroke was consequently defined as the AIRD-onset age.[24]

Patients were monitored through clinical visits or telephone interviews at 3, 6, and 12 months and annually after the HRMRI examination. Medical administration during follow-up period (including glucocorticoid, immune-suppressant, biological agent, and drugs for stroke prevention), and clinical outcomes (defined as any new stroke events, including ischemic stroke and hemorrhage, and death), were recorded.

Statistical Analysis

Patients were grouped according to the varied artery disease subtypes and AIRD subgroups, respectively. To increase consistency, only patients underwent contrasted-enhanced sequences were compared across etiology subtypes. Continuous variables were reported as mean ± standard deviation (SD) or median (interquartile range, IQR) depend on their distribution. Categorical variables were presented as numbers and percentages (*n*, %). The agreement between the readers were determined by calculation of Kappa Value (**Online Supplemental Table 2**). COX regression was conducted to estimate the cumulative stroke events-free rate. A value of $P < 0.05$ was deemed to indicate a statistically significant difference. All statistical analyses were executed using SPSS 26.0 software (IBM, Armonk, NY).

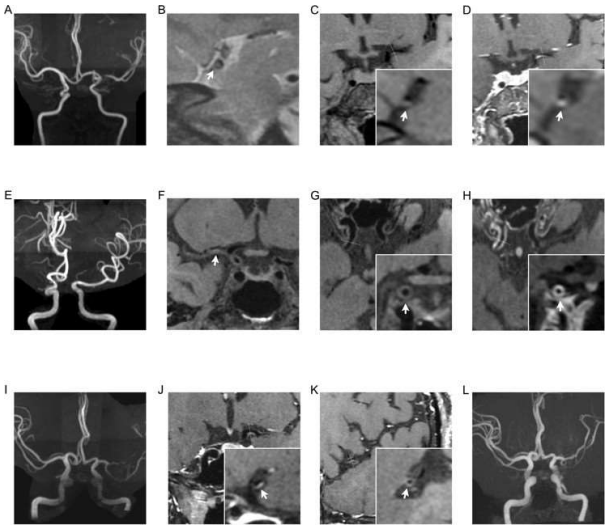
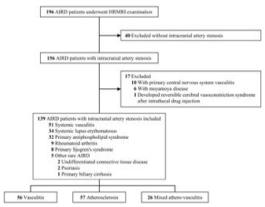


FIG 1. Three representative cases of ICAS associated with AIRD, as revealed by HRMRI.
(A-D) **Intracranial atherosclerosis**. MRA shows the left MCA stenosis associated with systemic lupus erythematosus (A). HRMRI reveals an eccentric wall thickening of left MCA in the coronal and sagittal planes (B and C, white arrow), accompanied by eccentric enhancement in the coronal and sagittal planes (D, white arrow), suggesting an atherosclerosis etiology.
(E–H) **Intracranial vasculitis**. MRA shows the right ICA stenosis and the right MCA occlusion associated with systematic vasculitis (E). HRMRI shows right MCA thrombus in the coronal plane (F, white arrow), a concentric wall thickening (G, white arrow) and concentric enhancement of right ICA C6 segment (H, white arrow) in the axial and coronal planes, suggesting a vasculitis etiology.
(I-L) **Mixed athero-vasculitis**. MRA shows the left MCA stenosis associated with primary antiphospholipid syndrome (I). HRMRI shows an eccentric wall thickening and eccentric enhancement of the left MCA M1 segment in the coronal and sagittal planes (J, white arrow), accompanied by a concentric wall thickening and concentric enhancement of the left MCA M2 segment (K, white arrow), suggesting a mixed athero-vasculitis etiology. The follow-up MRA shows regression of artery stenosis after immunosuppressive and antithrombotic therapy (L).
ICAS = intracranial artery stenosis; AIRD = autoimmune rheumatic diseases; HRMRI = high-resolution magnetic resonance imaging.

RESULTS

A total of 196 AIRD patients underwent HRMRI examination, of which 156 AIRD presented with ICAS. After excluding 10 patients with primary central nervous system vasculitis, 6 with moyamoya disease, and 1 patient with Sjogren's syndrome who developed reversible cerebral vasoconstriction syndrome after intrathecal drug injection, the data of 139 AIRD patients with ICAS were ultimately analyzed (**Fig 2**). Among them, 51 were diagnosed with systemic vasculitis (25 with large-vessel vasculitis, 18 with medium-small vessel vasculitis, and 8 with Behcet disease), 34 were systemic lupus erythematosus, 32 were primary antiphospholipid syndrome, 9 were rheumatoid arthritis, 8 were primary Sjogren's syndrome, and 5 were other rare AIRD (2 with psoriasis, 2 with undifferentiated connective tissue disease, and 1 with primary biliary cirrhosis). Eighty-nine patients underwent contrast-enhanced imaging.

Fig 2. Flow chart. AIRD = autoimmune rheumatic diseases; HRMRI = high-resolution magnetic resonance imaging.



Clinical Characteristics

As shown in **Online Supplemental Table 3**, the mean age at HRMRI examination was 45.1 years, the mean age of AIRD-onset was 39.9 years, and 90 (64.7%) were female. One hundred and ten (79.1%) patients had a history of stroke, including 2 patients with both ischemic stroke and hemorrhage, and 93 cases (66.9%) were attributed to symptomatic ICAS. Forty-four (31.7%) patients with intracranial artery occlusion. There were 56 (40.3%) patients diagnosed with intracranial vasculitis, 57 (41.0%) with atherosclerosis, and 26 (18.7%) with mixed athero-vasculitis.

As shown in **Online Supplemental Table 4**, patients with vasculitis experienced an AIRD-onset (34.5 years old vs. 42.9 and 45.0, P=0.010) and stroke-onset (36.8 years old vs. 45.5 and 47.3, P=0.019), nearly ten years earlier than patients with atherosclerosis and those with mixed athero-vasculitis other groups, and were more likely to have artery occlusion (44.6% vs. 21.1% and 26.9%, P=0.021). Patients with atherosclerosis demonstrated the highest cardiovascular risk factors exposure (73.7% vs. 48.2% in the vasculitis group and 61.5% in the mixed athero-vasculitis group, P=0.021) and lowest incidence of intracranial artery wall enhancement (63.2% vs. 100.0% in others, P<0.001). Patients with mixed athero-vasculitis were more likely to be male (69.2% vs. 30.4% in the vasculitis group and 24.6% in the atherosclerosis group, P<0.001), smoker (34.6% vs. 10.7% in the vasculitis group and 14.0% in the atherosclerosis group, P=0.040), and exhibited the greatest arteries involvement (mean 5 arteries/person vs. 3 in the vasculitis group and 2 in the atherosclerosis group, P<0.001). The results for patients who underwent with contrasted-enhanced sequences were compared across etiology subtypes and were presented in **Online Supplemental Table 5**.

When analyzing the AIRD subgroups, patients with systemic vasculitis were more likely to have intracranial vasculitis than intracranial atherosclerosis (49.0% vs. 25.5%), while patients with primary antiphospholipid syndrome were on the contrary (21.9% vs. 53.1%). In patients with systemic lupus erythematosus, both intracranial vasculitis (52.9%) and atherosclerosis (41.2%) were observed frequently.

Treatment and Clinical Outcomes

A total of 135 patients completed follow-up with a median of 21 (12-51) months. Among them, 73 (54.1%) patients were administered glucocorticoids, 83 (61.5%) received immune-suppressants and 10 (7.4%) were treated with biological agents. For stroke prevention, 96 (71.1%) were prescribed antithrombotic drugs and 93 (68.9%) were prescribed lipid-lowering agents. As shown in **Table 2**, maintenance therapy with glucocorticoids was more common among patients with vasculitis (72.2%), while fewer AIRD patients (46.4%) with intracranial atherosclerosis received immune-suppressant therapy. Forty-four patients completed the vascular imaging follow-up with a median of 20 (12-40) months, including 20 HRMRI follow-ups. No subtype changes among vasculitis, atherosclerosis, and mixed athero-vasculitis were observed. The majority of patients remained stable, while 9 (20.5%) patients had artery stenosis regression and 5 (11.4%) had artery stenosis progression.

During the follow-up period, 23 (17.0%) patients experienced stroke events, including 21 ischemic strokes and 2 intracranial hemorrhages, all of whom had a history of stroke. Eight (5.9%) patients died, of whom 7 had a history of stroke, and 4 experienced ischemic stroke events during follow-up. Regarding the causes of death, 6 were attributed to infection and the other 2 remained unknown. Patients with mixed athero-vasculitis had the highest incidence of stroke events (32.0%), while patients with intracranial atherosclerosis had the lowest (10.7%). After adjusting age and gender, there were no significant differences concerning stroke events during follow-up among etiology subtypes, with the exception of a higher incidence of stroke events in patients with mixed athero-vasculitis than patients with atherosclerosis (HR 3.146, 95% CI 1.033 to 9.585, P=0.044, **Fig 3**). Patients with mixed athero-vasculitis had the highest mortality (12.0%).

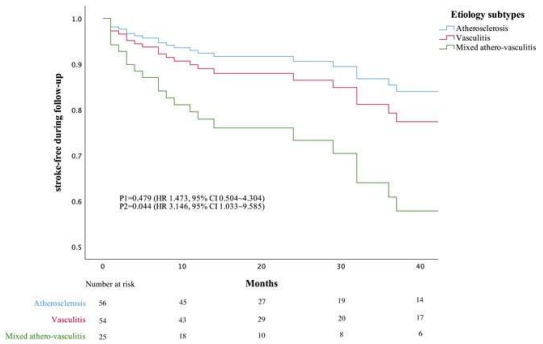


Fig 3. COX regression of stroke-free rate during follow-up between etiology subtypes.
P1= Vasculitis vs. Atherosclerosis; P2= Mixed athero-vasculitis vs. Atherosclerosis.

DISCUSSION

This study conducted a systematic investigation into the clinical characteristics and outcomes of three imaging-defined etiologies of ICAS associated with AIRD, including atherosclerosis, vasculitis, and mixed athero-vasculitis. Patients with vasculitis experienced the earliest AIRD-onset but were most likely to have artery occlusion. Patients with atherosclerosis exhibited the highest cardiovascular risk factors exposure and showed less intracranial artery wall enhancement. Patients with mixed athero-vasculitis constituted the only subtype with male preponderance and exhibited the most artery involvement. During follow-up, patients with mixed athero-vasculitis experienced the highest stroke event risk and the highest mortality.

In previous studies, ICAS was reported in AIRD patients with or without stroke.[5, 6] The detailed clinical characteristics and etiology, however, have been largely elusive. In our study cohort, the mean age at HRMRI examination was 45.1 years, merely 5 years subsequent to the initial symptoms of AIRD, suggesting that intracranial vascular damage could occur in the early-life and early stage of the diseases. It may be also partly due to the high percentage (61.2%) of patients exposed to coexistent cardiovascular risk factors exposure, which accelerates vascular damages in AIRD. Should intracranial vasculitis as the predominant etiology, it is posited that inflammation encompassing all arterial layers could induce wall edema, endothelium hyperplasia and thrombosis formation. These factors collectively exert synergistic effects, exacerbating stenosis severity and precipitating early arterial occlusion.[25] It was anticipated that patients with atherosclerosis were older, and exhibited a higher proportion of cardiovascular risk factors exposure than those with vasculitis.[26] Nevertheless, the mean age of 49.3 years old, and a high percentage of stroke history (80.7%) suggested these individuals may suffer from premature atherosclerosis, making them more susceptible to stroke than the general population.[27] The novel finding was that nearly one-fifth of our patients exhibited mixed athero-vasculitis. They had similar age as the patients with atherosclerosis yet demonstrated comparable intracranial artery wall enhancement (100%) on HRMRI as the patients with vasculitis, indicating an overlap of atherosclerosis and vasculitis. Although previous studies reported that vasculitis may turn into atherosclerosis over time,[28] it was not supported by our follow-up imaging data. The characteristics of male dominance and multiple artery involvement imply that mixed athero-vasculitis may possess unique underlying mechanisms.

Atherosclerosis was observed more frequently in patients with primary antiphospholipid syndrome but less frequently in patients with systemic vasculitis, potentially due to the different pathophysiology of the two diseases. Endothelial dysfunction, mediated by autoantibodies, is recognized as the initial factor in primary antiphospholipid syndrome. This, combined with the co-action of cardiovascular risk factors, promotes the macrophage uptake of oxidized low lipid density lipoprotein and deposition under the intima, gradually developing atherosclerosis plaque;[29] while systemic vasculitis is characterized as artery inflammation, is attributed to the immune complexes, mainly situated in the media and adventitia.[30] That may elucidate why intracranial atherosclerosis was more prevalent in antiphospholipid syndrome. In systemic lupus erythematosus, the deposition of immune complexes may lead to vasculitis, while concurrent endothelial injury may result in atherosclerosis, particularly when combined with secondary antiphospholipid syndrome.[29, 31] As a result, both vasculitis and atherosclerosis were common in patients with systemic lupus erythematosus.

Nearly four-fifths of our patients had a history of stroke. During a median follow-up of 21 months, 17.0% of patients experienced stroke events and 5.9% succumbed died. Compared with the results in other young stroke studies, the incidence of stroke was much higher than that in the IPSYS study (3.2% at 1 year, 10.9% at 5 years),[32] and mirrored the findings of the FUTURE study (19.6%) with a longer follow-up of 9.1 years. [33] The results indicated that AIRD patients with ICAS were at high risk of stroke and death despite undergoing immune-suppressive and stroke prevention therapies. Timely initiation of more precise management is imperative. Patients with mixed athero-vasculitis exhibited the highest stroke recurrence risk and the highest mortality, suggesting they were required more aggressive management.

Our study has limitations. Firstly, this is a retrospective analysis. Selection bias may exist as patients with asymptomatic ICAS were less likely to be enrolled, future prospective studies are warranted to confirm our findings. Secondly, due to the infeasibility of the intracranial large artery tissue, the imaging-defined etiology, lacks the gold standard confirmation of pathological diagnosis, though evidence has been provided by several imaging-autopsy studies.[34, 35] Combining serum or cerebrospinal fluid biomarkers with HRMRI may further improve the diagnostic accuracy and monitor of disease activity in ICAS associated with AIRD.

CONCLUSIONS

In summary, our study suggests that intracranial arteries are injured and lead to heterogeneous disease courses when exposed to AIRD and cardiovascular risk factors. While atherosclerosis acceleration is common, vasculitis may further contribute to early-developed occlusion and multiple artery involvement. Varied intracranial arteriopathies may result in different outcomes.

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SUPPLEMENTAL FILES

Supplemental methods

Imaging analysis

The symptomatic ICAS was defined as the intracranial culprit artery with at least 50% stenosis, meanwhile excluding the other etiology (eg. Cardio-embolismic, extracranial carotid stenosis >50%).[1] For the artery with occlusion, the wall morphology in the distal or proximal artery was evaluated and considered to be the etiology of the occluded artery.

According to the TOSS grading system, the severity of ICAS were classified into 1 of 5 grades: normal, mild (signal reduction <50% stenosis), moderate (signal reduction ≥ 50%), severe (focal signal loss with the presence of distal flow), and occlusion (sudden cutoff without distal flow); Progression was defined as worsening in the degree of stenosis on the follow-up MRA in comparison with the baseline MRA, and regression was defined as improving of the degree of stenosis.[2]

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Online Supplemental Table 1: MR Imaging parameters

Sequences	T1WI	T2WI	FLAIR	DWI	T2*WI	HR-3D T1WI	HR-2D T2WI
GE discovery MR 750							
TR (ms)	1775	5258	12000	3600	42	800	3400
TE (ms)	21.6	84	122	64	23	15	56
FA (°)	111	142	160	90	20	90	—
Slice thickness (mm)	4	4	4	4	6	0.8	2
Number of slices	40	36	36	36	48	128	12
Acquisition matrix	320×160	320×320	288×192	128×128	480×288	320×256	384×256
FOV (mm^2)	240×168	220×220	220×176	220×220	240×220	204×184	130
Siemens skyra							
TR (ms)	2000	3300	8000	5100	26	800	3460
TE (ms)	11	117	117	94	19	15	65
FA (°)	150	90	150	180	20	120	150
Slice thickness (mm)	6	6	6	6	2	0.8	2
Number of slices	20	20	24	20	20	240	12
Acquisition matrix	320×224	384×384	320×224	160×160	320×224	256×256	384×256
FOV (mm^2)	—	—	—	—	—	—	—

Online Supplemental Table 2: Inter-reader and intra-reader reproducibility for imaging analysis

Indicators	K value (95% CI)	P value
Etiology subtypes		
Inter-reader agreement	0.909 (0.848-0.970)	<0.001
Intra-reader agreement	0.923 (0.868-0.978)	<0.001
Intracranial artery stenosis		
Inter-reader agreement	0.924 (0.899-0.993)	<0.001
Intra-reader agreement	0.946 (0.899-0.993)	<0.001
Intracranial artery wall enhancement		
Inter-reader agreement	0.726 (0.471-0.981)	<0.001
Intra-reader agreement	0.726 (0.471-0.981)	<0.001
Artery stenosis degree changes during follow-up		
Inter-reader agreement	0.847 (0.681-1.000)	<0.001
Intra-reader agreement	0.905 (0.778-1.000)	<0.001

Online Supplemental Table 3: Description of clinical characteristics and outcomes in AIRD subgroups.

Characteristics	Total (N=139)	Systemic vasculitis (n=51)	Primary APS (n=32)	SLE (n=34)	RA (n=9)	SS (n=8)	Other (n=5)
Age, mean (SD)	45.1 (17.3)	44.2 (18.7)	40.3 (12.7)	41.5 (18.2)	59.4 (9.2)	60.5 (12.0)	58.2 (11.1)
AIRD-onset age, mean (SD)	39.9 (17.5)	40.2 (18.4)	37.8 (12.8)	34.2 (18.9)	47.5 (11.1)	55.4 (15.9)	55.5 (13.5)
Stroke-onset age, mean (SD)	42.4 (16.9)	43.5 (18.2)	38.6 (13.1)	38.0 (18.1)	57.2 (3.7)	58.8 (11.3)	55.0 (15.5)
Female, n (%)	90 (64.7)	28 (54.9)	18 (56.3)	29 (85.3)	6 (66.7)	8 (100.0)	1 (20.0)
Any risk factors, n (%)	85 (61.2)	29 (56.9)	20 (62.5)	20 (58.8)	7 (77.8)	6 (75.0)	3 (60.0)
Hypertension	60 (43.2)	19 (37.3)	16 (50.0)	13 (38.2)	4 (44.4)	5 (62.5)	3 (60.0)
Hyperlipidemia	35 (25.2)	10 (19.6)	9 (28.1)	10 (29.4)	2 (22.2)	2 (25.0)	2 (40.0)
Diabetes	28 (20.1)	13 (25.5)	7 (21.9)	4 (11.8)	3 (33.3)	0	1 (20.0)
Smoking	23 (16.5)	11 (21.6)	5 (15.6)	4 (11.8)	1 (11.1)	1 (12.5)	1 (20.0)
History of stroke, n (%)	110 (79.1)	35 (68.6)	30 (93.8)	30 (88.2)	5 (55.6)	6 (75.0)	4 (80.0)
Subtypes, n (%)							
Atherosclerosis	57 (41.0)	13 (25.5)	17 (53.1)	14 (41.2)	7 (77.8)	4 (50.0)	2 (40.0)
Vasculitis	56 (40.3)	25 (49.0)	7 (21.9)	18 (52.9)	1 (11.1)	3 (37.5)	2 (40.0)
Mixed athero-vasculitis	26 (18.7)	13 (25.5)	8 (25.0)	2 (5.9)	1 (11.1)	1 (12.5)	1 (20.0)
Symptomatic ICAS, n (%)	93 (66.9)	30 (58.8)	27 (84.4)	25 (73.5)	5 (55.6)	3 (37.5)	3 (60.0)
Intracranial artery occlusion, n (%)	44 (31.7)	10 (19.6)	13 (40.6)	13 (38.2)	2 (22.2)	3 (37.5)	3 (60.0)
Numbers of intracranial stenotic artery	3 (2-6)	3 (2-6)	3 (2-6)	3 (1-5)	2 (2-3)	3 (2-5)	5 (3-6)
Intracranial artery wall enhancement, n (%)	82/89 (92.1)	40/41 (97.6)	14/18 (77.8)	21/23 (91.3)	2/2 (100.0)	3/3 (100.0)	2/2 (100.0)
Follow-up, n (%)	135 (97.1)	50 (98.0)	31 (96.9)	33 (97.1)	8 (88.9)	8 (100.0)	5 (100.0)
Follow-up time interval (month)	21 (12-51)	19 (12-30)	20 (12-39)	21 (12-67)	45 (10-55)	68 (10-80)	29 (14-30)
Medicine administration, n (%)							
Antithrombotic drugs	96 (71.1)	29 (58.0)	28 (90.3)	28 (84.8)	4 (50.0)	4 (50.0)	3 (60.0)
Lipid-lowering agent	93 (68.9)	28 (56.0)	26 (83.9)	23 (69.7)	6 (75.0)	6 (75.0)	4 (80.0)
Glucocorticoid	73 (54.1)	33 (66.0)	9 (29.0)	26 (78.8)	2 (25.0)	3 (37.5)	0
Immune-suppressant	83 (61.5)	35 (70.0)	13 (41.9)	26 (78.8)	3 (37.5)	3 (37.5)	3 (60.0)
Biological agent	10 (7.4)	8 (16.0)	0	1 (3.0)	1 (12.5)	0	0
Clinical outcomes							
Stroke events, n (%)	23 (17.0)	6 (12.0)	9 (29.0)	8 (24.2)	0	0	0
Ischemic stroke and TIA	21 (15.6)	5 (10.0)	9 (29.0)	7 (21.2)	0	0	0
Hemorrhage	2 (1.5)	1 (2.0)	0	1 (3.0)	0	0	0
Death, n (%)	8 (5.9)	7 (14.0)	0	1 (3.0)	0	0	0

AIRD = autoimmune rheumatic diseases; APS = antiphospholipid syndrome; SLE = systemic lupus erythematosus; RA = rheumatoid arthritis; SS = Sjogren's syndrome; SD = standard deviation; ICAS = intracranial artery stenosis; TIA = transient ischemic attack.

Online Supplemental Table 4: Description of clinical characteristics between the etiology subtypes of ICAS associated with AIRD.

Characteristics	Vasculitis (n=56)	Atherosclerosis (n=57)	Mixed athero-vasculitis (n=26)	P value
Age, mean (SD)	38.4 (18.6)	49.3 (15.0)	50.0 (15.2)	0.001
AIRD-onset age, mean (SD)	34.5 (19.4)	42.9 (15.5)	45.0 (14.3)	0.010
Stroke-onset age, mean (SD)	36.8 (17.2)	45.5 (15.7)	47.3 (16.1)	0.019
Female, n (%)	39 (69.6)	43 (75.4)	8 (30.8)	<0.001
Any risk factors, n (%)	27 (48.2)	42 (73.7)	16 (61.5)	0.021
Hypertension	17 (30.4)	29 (50.9)	14 (53.8)	0.045
Hyperlipidemia	12 (21.4)	16 (28.1)	7 (26.9)	0.714
Diabetes	9 (16.1)	13 (22.8)	6 (23.1)	0.646
Smoking	6 (10.7)	8 (14.0)	9 (34.6)	0.040
History of stroke, n (%)	44 (78.6)	46 (80.7)	20 (76.9)	0.927
Symptomatic ICAS, n (%)	40 (71.4)	35 (61.4)	18 (69.2)	0.530
Intracranial artery occlusion, n (%)	25 (44.6)	12 (21.1)	7 (26.9)	0.021
Numbers of intracranial stenotic artery	3 (1-5)	2 (1-5)	5 (3-6)	0.001
Intracranial artery wall enhancement, n (%)	45/45 (100.0)	12/19 (63.2)	25/25 (100.0)	<0.001
Follow-up, n (%)	54 (96.4)	56 (98.2)	25 (96.2)	
Follow-up time interval (month)	21 (12-60)	20 (11-48)	22 (14-42)	
Medicine administration, n (%)				
Antithrombotic drugs	41 (75.9)	37 (66.1)	18 (72.0)	0.509
Lipid-lowering agent	35 (64.8)	40 (71.4)	18 (72.0)	0.735
Glucocorticoid	39 (72.2)	23 (41.1)	11 (44.0)	0.002
Immune-suppressants	41 (75.9)	26 (46.4)	16 (64.0)	0.005
Biological agent	6 (11.1)	1 (1.8)	3 (12.0)	0.074
Clinical outcomes				
Stroke events, n (%)	9 (16.7)	6 (10.7)	8 (32.0)	0.077
Ischemic stroke or TIA	8 (14.8)	6 (10.7)	7 (28.0)	
Hemorrhage	1 (1.9)	0	1 (4.0)	
Death, n (%)	2 (3.7)	3 (5.4)	3 (12.0)	0.356
Imaging follow-up	20	17	7	
Imaging follow-up time interval (month)	20 (10-47)	22 (13-44)	18 (10-24)	
Artery stenosis degree changes, n (%)				0.679
Regression	4 (20.0)	3 (17.6)	2 (28.6)	
Stable	15 (75.0)	11 (64.7)	4 (57.1)	
Progression	1 (5.0)	3 (17.6)	1 (14.3)	

ICAS = intracranial artery stenosis; AIRD = autoimmune rheumatic diseases; SD = standard deviation; TIA = transient ischemic attack.

Online Supplemental Table 5: Description of clinical characteristics between the etiology subtypes in AIRD patients with contrast-enhanced imagings.

Characteristics	Total (N=89)	Vasculitis (n=45)	Atherosclerosis (n=19)	Mixed athero-vasculitis (n=25)	P value
Age, mean (SD)	42.7 (17.0)	38.0 (17.7)	43.6 (14.0)	50.5 (17.0)	0.011
AIRD-onset age, mean (SD)	38.6 (17.5)	34.3 (19.1)	39.2 (15.0)	45.6 (14.5)	0.033
Stroke-onset age, mean (SD)	40.5 (16.8)	36.6 (16.6)	39.7 (15.7)	48.0 (16.3)	0.057
Female, n (%)	53 (59.6)	30 (66.7)	15 (78.9)	8 (32.0)	0.002
Any risk factors, n (%)	48 (53.9)	22 (48.9)	10 (52.6)	16 (64.0)	0.485
Hypertension	35 (39.3)	14 (31.1)	7 (36.8)	14 (56.0)	0.125
Hyperlipidemia	19 (21.3)	9 (20.0)	3 (15.8)	7 (28.0)	0.586
Diabetes	18 (20.2)	7 (15.6)	5 (26.3)	6 (24.0)	0.607
Smoking	19 (21.3)	6 (13.3)	4 (21.1)	9 (36.0)	0.102
History of stroke, n (%)	69 (77.5)	35 (77.8)	15(78.9)	19 (76.0)	1.000
Symptomatic ICAS, n (%)	61 (68.5)	32 (71.1)	12 (63.2)	17 (68.0)	0.833
Intracranial artery occlusion, n (%)	26 (29.2)	17 (37.8)	3 (15.8)	6 (24.0)	0.197
Numbers of intracranial stenotic artery	4 (2-6)	3 (2-5)	3 (1-5)	5 (3-6)	0.026
Intracranial artery wall enhancement, n (%)	82 (92.1)	45 (100.0)	12 (63.2)	25 (100.0)	<0.001
Follow-up, n (%)	88 (98.9)	44 (97.8)	19 (100.0)	25 (100.0)	
Follow-up time interval (month)	21 (11-50)	21 (12-55)	24 (10-44)	22 (14-42)	
Medicine administration, n (%)					
Antithrombotic drugs	65 (73.9)	34 (77.3)	13 (68.4)	18 (72.0)	0.772
Lipid-lowering agent	57 (64.8)	28 (63.6)	11 (57.9)	18 (72.0)	0.615
Glucocorticoid	56 (63.6)	35 (79.5)	10 (52.6)	11 (44.0)	0.006
Immune-suppressants	65 (73.9)	34 (77.3)	15 (78.9)	16 (64.0)	0.437
Biological agent	9 (10.2)	5 (11.4)	1 (5.3)	3 (12.0)	0.809
Clinical outcomes					
Stroke events, n (%)	17 (19.3)	6 (13.6)	3 (15.8)	8 (32.0)	0.185
Ischemic stroke or TIA	15 (17.0)	5 (11.4)	3 (15.8)	7 (28.0)	
Hemorrhage	2 (2.3)	1 (2.3)	0	1 (4.0)	
Death, n (%)	6 (6.8)	2 (4.5)	1 (5.3)	3 (12.0)	0.548
Imaging follow-up	31	18	6	7	
Imaging follow-up time interval (month)	20 (12-50)	20 (9-49)	37 (17-51)	18 (10-24)	
Artery stenosis degree changes, n (%)					0.209
Regression	6 (19.4)	4 (22.2)	0	2 (28.6)	
Stable	23 (74.2)	14 (77.8)	5 (83.3)	4 (57.1)	
Progression	2 (6.5)	0	1 (16.7)	1 (14.3)	

AIRD = autoimmune rheumatic diseases; SD = standard deviation; ICAS = intracranial artery stenosis; TIA = transient ischemic attack.