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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: Using data from a high-resolution MR imaging database, we retrospectively reviewed patients with AIRD with ICAS. Stratification into vasculitis, atherosclerosis, and mixed atherovasculitis subtypes was based on imaging findings, followed by a comparative analysis of clinical characteristics and outcomes across these subgroups.

RESULTS: Among 139 patients (mean, 45.1 [SD, 17.3] years; 64.7% women), 56 (40.3%) were identified with vasculitis; 57 (41.0%), with atherosclerosis; and 26 (18.7%), with mixed atherovasculitis. The average interval from AIRD onset to high-resolution MRI was 5 years. Patients with vasculitis presented at a younger age of AIRD onset (mean, 34.5 [SD, 19.4] years), nearly 10 years earlier than other groups ($P = .010$), with a higher artery occlusion incidence (44.6% versus 21.1% and 26.9%, $P = .021$). Patients with atherosclerosis showed the highest cardiovascular risk factor prevalence (73.7% versus 48.2% and 61.5%, $P = .021$) but fewer intracranial artery wall enhancement instances (63.2% versus 100% in others, $P < .001$). The mixed atherovasculitis group, predominantly men (69.2% versus 30.4% and 24.6%, $P < .001$), exhibited the most arterial involvement (5 arteries per person versus 3 and 2, $P = .001$). Over an average 21-month follow-up, 23 (17.0%) patients experienced stroke events and 8 (5.9%) died, with the mixed atherovasculitis 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 the early development of occlusion and multiple artery involvement. Varied intracranial arteriopathies may result in different outcomes.

ABBREVIATIONS: AIRD = autoimmune rheumatic diseases; HRMRI = high-resolution MRI; ICAS = intracranial artery stenosis

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, Sjogren syndrome, and so forth.[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 are 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 patients with AIRD at a young age.[5,6] However, the underlying pathophysiology remains insufficiently studied, in part due to the difficulties in establishing an etiologic diagnosis through conventional lumen imaging. Whether it involves intracranial

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SUMMARY

PREVIOUS LITERATURE: AIRD can cause 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 atherovasculitis, 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 worse outcomes.

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

vasculitis or atherosclerosis, ICAS may manifest as segmental artery narrowing and poststenotic dilation on MRA, CTA, or DSA.[7] The uncertain etiology greatly complicates clinical decision-making and leads to confused treatment.

In the last decade, high-resolution MR imaging (HRMRI) has emerged as a noninvasive 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 patients with AIRD using HRMRI and compare the differences in the clinical characteristics and outcomes across the etiology subgroups. This article follows the STrengthening the Reporting of OBservational studies in Epidemiology (STROBE) guidelines.

MATERIALS AND METHODS

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

Patient Selection

Patients were included if they fulfilled the following criteria; 1) had ICAS on MRA (including the C6/C7 segment of the ICA, the M1/M2 segment of the MCA, the A1 segment of the anterior cerebral artery, the V4 segment of the vertebral artery, the basilar artery, and the P1 segment of the posterior cerebral artery; and 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-quality images were excluded. Exclusion criteria also encompassed patients diagnosed with primary CNS vasculitis, Moyamoya disease, and reversible cerebral vasoconstriction syndrome, which were attributed to the high heterogeneity of etiologies in addition to AIRD.[7,16,17]

Imaging Protocol

All MRIs were obtained on two 3T systems (Cube, GE Healthcare; and sampling perfection with application-optimized contrasts by using different flip angle evolutions [SPACE], Siemens), following the standardized protocol.[18,19] The protocol included conventional 3D TOF-MRA, DWI, ADC, 3D T1-weighted head-neck joint HRMRI, and 2D T2-weighted vessel wall imaging of the MCA. Contrast enhancement was applied selectively to 3D T1WI (Cube system) following gadolinium administration (0.01 mmol/Kg of gadopentetate dimeglumine). The imaging parameters are listed in the Online Supplemental Data.

Imaging Definition

Image analysis was performed on each stenotic artery, and individuals were categorized into 3 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 on visual inspection;[18] 2) vasculitis, characterized by concentric stenosis in the orthogonal plane, potentially accompanied by concentric enhancement following gadolinium administration;[20] and 3) mixed atherovasculitis, 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 Warfarin-Aspirin Symptomatic Intracranial Disease (WASID) criteria.[22] On 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; http://www.osirix-viewer.com) by 2 readers (S.L. and M.L., with 8 and 20 years of experience, respectively). Should a disagreement arise, a third reader (W.X., 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, sex, 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

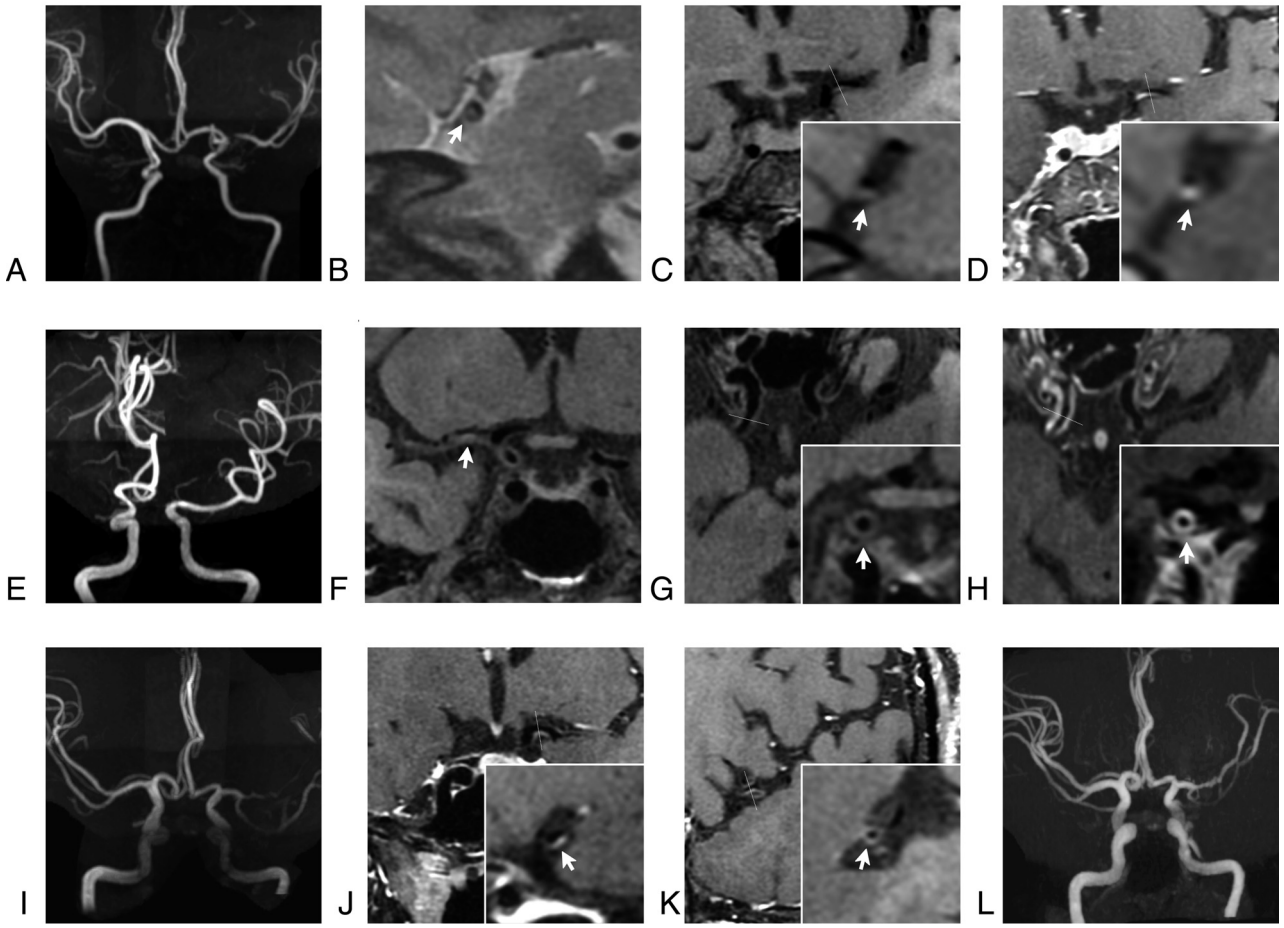

FIG 1. Three representative cases of ICAS associated with AIRD, as revealed by HRMRI. *A–D*, Intracranial atherosclerosis. MRA shows the left MCA stenosis associated with systemic lupus erythematosus (*A*). HRMRI reveals an eccentric wall thickening of the left MCA in the coronal and sagittal planes (*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 right ICA stenosis and 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 the right ICA C6 segment (*H*, *white arrow*) in the axial and coronal planes, suggesting a vasculitis etiology. *I–L*, Mixed atherovasculitis. 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 atherovasculitis etiology. The follow-up MRA shows regression of arterial stenosis after immunosuppressive and antithrombotic therapy (*L*).

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. Administration of medications during the follow-up period (including glucocorticoid, immune-suppressant, biologic agents, 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. Continuous variables were reported as mean (SD) or median (interquartile range), depending on their distribution. Categoric variables were presented as numbers and percentages. Cox regression was conducted to estimate the cumulative stroke event-free rate. A value of $P < .05$ indicated a statistically significant difference. All statistical analyses were conducted using SPSS 26.0 software (IBM).

RESULTS

A total of 196 patients with AIRD underwent HRMRI examinations, of whom 156 with AIRD presented with ICAS. After excluding 10 patients with primary CNS vasculitis, 6 with Moyamoya disease, and 1 patient with Sjogren syndrome who developed reversible cerebral vasoconstriction syndrome after intrathecal drug injection, the data of 139 patients with AIRD 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 with systemic lupus erythematosus; 32 with primary antiphospholipid syndrome; 9 with rheumatoid

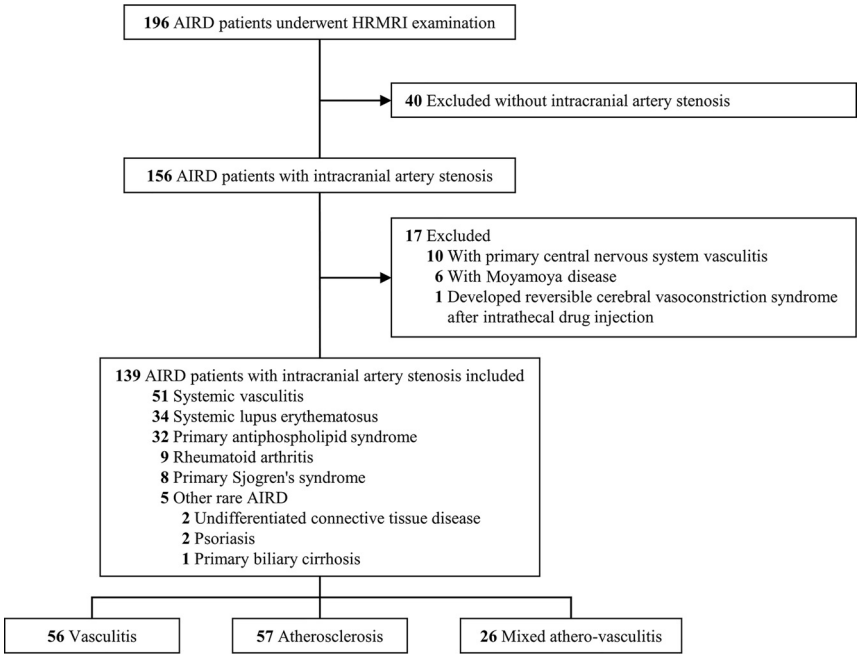

FIG 2. Flow chart.

arthritis; 8 with primary Sjogren syndrome; and 5 with 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.

Clinical Characteristics

As shown in the Online Supplemental Data, 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 women. One hundred 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 had intracranial artery occlusion. There were 56 (40.3%) patients diagnosed with intracranial vasculitis; 57 (41.0%), with atherosclerosis; and 26 (18.7%), with mixed atherovasculitis.

As shown in the Online Supplemental Data, patients with vasculitis experienced an AIRD onset (34.5 versus 42.9 and 45.0 years old, $P = .010$) and stroke onset (36.8 versus 45.5 and 47.3 years old, $P = .019$) nearly ten years earlier than patients with atherosclerosis and those with mixed atherovasculitis, and were more likely to have artery occlusion (44.6% versus 21.1% and 26.9%, $P = .021$). Patients with atherosclerosis demonstrated the highest cardiovascular risk factor exposure (73.7% versus 48.2% in the vasculitis group and 61.5% in the mixed atherovasculitis group, $P = .021$) and the lowest incidence of intracranial artery wall enhancement (63.2% versus 100.0% in others, $P < .001$). Patients with mixed atherovasculitis were more likely to be men (69.2% versus 30.4% in the vasculitis group and 24.6% in the atherosclerosis group, $P < .001$), smokers (34.6% versus 10.7% in the vasculitis group and 14.0% in the atherosclerosis group, $P = .040$), and exhibit the greatest artery involvement (mean, 5 arteries/person versus 3 in the vasculitis group and 2 in the atherosclerosis group, $P < .001$).

When analyzing the AIRD subgroups, patients with systemic vasculitis were more likely to have intracranial vasculitis than intracranial atherosclerosis (49.0% versus 25.5%), while patients with primary antiphospholipid syndrome were on the contrary (21.9% versus 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 (range, 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 biologic agents. For stroke prevention, 96 (71.1%) were prescribed antithrombotic drugs and 93 (68.9%) were prescribed lipid-lowering agents. As shown in the Online Supplemental Data, maintenance therapy with glucocorticoids was more common among patients with vasculitis (72.2%), while fewer patients with AIRD (46.4%) with intracranial atherosclerosis received immune-suppressant therapy. Forty-four patients completed the vascular imaging follow-up, with a median of 20 (range, 12–40) months, including 20 HRMRI follow-ups. No subtype changes among vasculitis, atherosclerosis, and mixed atherovasculitis were observed. Most 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 deaths were attributed to infection and the other 2 remained unknown. Patients with mixed atherovasculitis had the highest incidence of stroke events (32.0%), while patients with intracranial atherosclerosis had the lowest (10.7%). After adjusting for age and sex, 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 atherovasculitis than patients with atherosclerosis (HR, 3.146; 95% CI, 1.033–9.585, $P = .044$, Fig 3). Patients with mixed atherovasculitis had the highest mortality (12.0%).

DISCUSSION

We conducted a systematic investigation into the clinical characteristics and outcomes of 3 imaging-defined etiologies of ICAS associated with AIRD, including atherosclerosis, vasculitis, and mixed atherovasculitis. Patients with vasculitis experienced the earliest AIRD onset but were more likely to have artery occlusion.

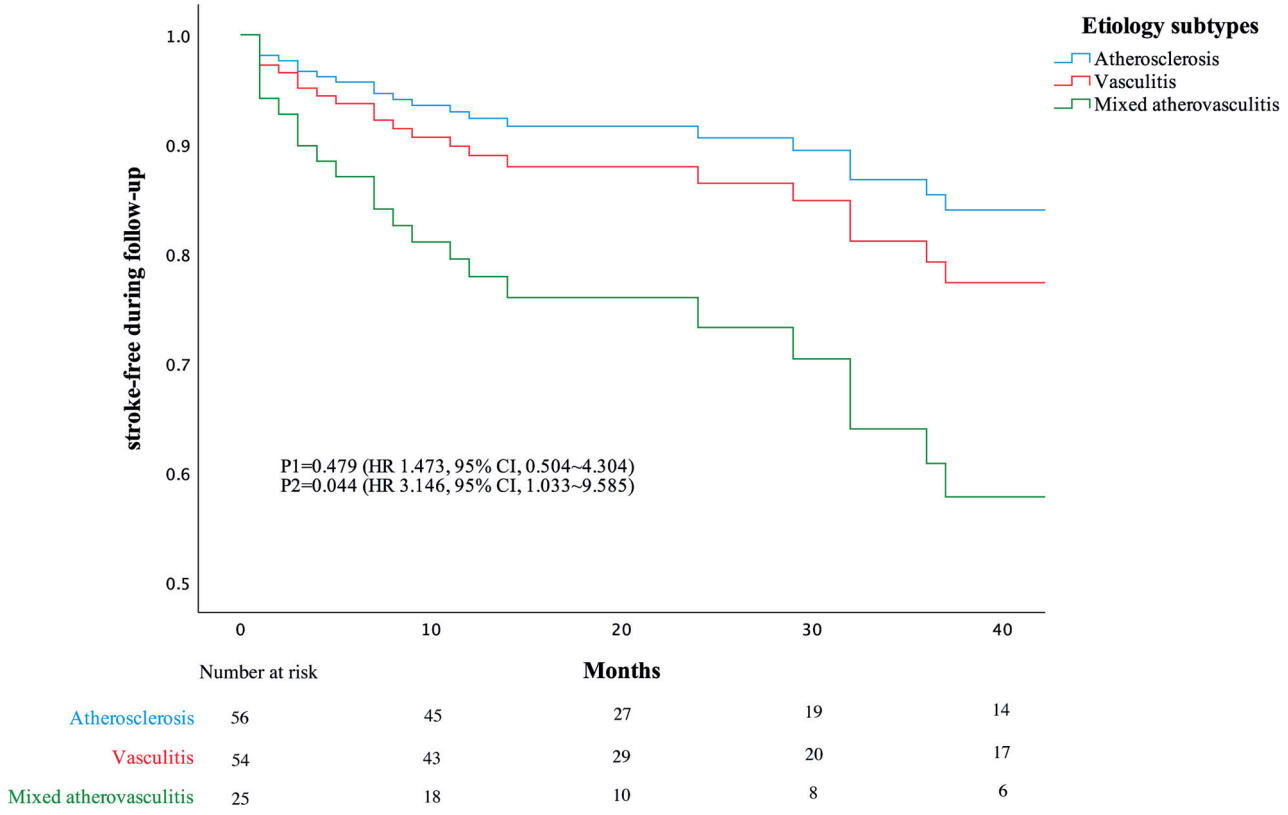

FIG 3. Cox regression of the stroke-free rate during follow-up among etiology subtypes. P1 indicates vasculitis versus atherosclerosis; P2, mixed atherovasculitis versus atherosclerosis.

Patients with atherosclerosis exhibited the highest cardiovascular risk factor exposure and showed less intracranial artery wall enhancement. Patients with mixed atherovasculitis constituted the only subtype with male preponderance and exhibited the most artery involvement. During follow-up, patients with mixed atherovasculitis experienced the highest stroke event risk and the highest mortality.

In previous studies, ICAS was reported in patients with AIRD 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 early life and the early stage of the disease. It may be also partly due to the high percentage (61.2%) of patients exposed to coexistent cardiovascular risk factors, which accelerates vascular damage in AIRD. Should intracranial vasculitis be 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 factor exposure than those with vasculitis.[26] Nevertheless, the mean age of 49.3 years and a high percentage of stroke history (80.7%) suggested that these individuals may have 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 atherovasculitis. Their age was similar to that in patients with atherosclerosis, yet they demonstrated intracranial artery wall enhancement (100%) on HRMRI comparable with that in the patients with vasculitis, indicating an overlap of atherosclerosis and vasculitis. Although previous studies reported that vasculitis may turn into atherosclerosis with time,[28] this outcome was not supported by our follow-up imaging data. The characteristics of male dominance and multiple artery involvement imply that mixed atherovasculitis may have 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 2 diseases. Endothelial dysfunction, mediated by autoantibodies, is recognized as the initial factor in primary antiphospholipid syndrome. This, combined with the coaction of cardiovascular risk factors, promotes the macrophage uptake of oxidized low-density lipoprotein and deposition under the intima, gradually developing into atherosclerosis plaque,[29] while systemic vasculitis is characterized as artery inflammation and is attributed to the immune complexes, mainly situated in the media and adventitia.[30] That explanation 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% died. Compared with the results in other studies of young individuals with stroke, the incidence of stroke was much higher than that in the Italian Project on Stroke in Young Adults study (3.2% at 1 year, 10.9% at 5 years)[32] and mirrored the findings of the Follow-Up of Transient ischemic attack and stroke patients and Unelucidated Risk factor Evaluation (FUTURE) study (19.6%), with a longer follow-up of 9.1 years.[33] The results indicated that patients with AIRD 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 atherovasculitis exhibited the highest stroke-recurrence risk and the highest mortality, suggesting that they required more aggressive management.

Our study has limitations. First, this was a retrospective analysis. Selection bias may exist because patients with asymptomatic ICAS were less likely to be enrolled; future prospective studies are warranted to confirm our findings. Second, due to the infeasibility of the intracranial large-artery tissue, the imaging-defined etiology lacks the criterion standard confirmation of pathologic diagnosis, though evidence has been provided by several imaging postmortem studies.[34,35] Combining serum or CSF biomarkers with HRMRI may further improve the diagnostic accuracy and monitoring of disease activity in ICAS associated with AIRD.

CONCLUSIONS

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

Disclosure forms provided by the authors are available with the full text and PDF of this article at www.ajnr.org.

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