Isolated MCA Disease in Patients Without Significant Atherosclerotic Risk Factors
A High-Resolution Magnetic Resonance Imaging Study

Sung-Ho Ahn, MD; Jookyung Lee, MD; Yeon-Jung Kim, MD; Sun U. Kwon, MD, PhD; Deokhee Lee, MD, PhD; Seung-Chai Jung, MD, PhD; Dong-Wha Kang, MD, PhD; Jong S. Kim, MD, PhD

Background and Purpose—Diagnosis of intracranial artery atherosclerosis remains often uncertain. The high-resolution magnetic resonance imaging (HR-MRI) enables vessel wall assessment for more precise diagnoses. The aim of the present study was to investigate the etiologies of middle cerebral artery steno-occlusive disease in young adult patients with few atherosclerotic risk factors using HR-MRI.

Methods—We prospectively studied patients who visited a tertiary hospital in Seoul, Korea, and had (1) unilateral middle cerebral artery disease (≥50% stenosis or occlusion), (2) were ≤55 years old and had no or minimal (≤1) atherosclerotic risk factors. We excluded patients with a confirmed diagnosis of Moyamoya disease, vasculitis, or dissection and those having embolic sources. A presumptive diagnosis was made based on HR-MRI findings, and patients were categorized as HR-athero (atherosclerotic disease), HR-MMD (Moyamoya disease), HR-dissection, or HR-vasculitis.

Results—Among 95 patients analyzed, 26 (27.4%) had HR-athero who were more often male (P=0.004), smokers (P=0.018), and had focal stenosis (P=0.003) than others. As compared with the HR-athero patients, 29 hours-MMD patients were more often female (P<0.001) and more often had occlusive lesions (P=0.001) and nonfocal stenosis (P<0.001). The 22 hours-dissection patients tended to have hypertension less often, and the 13 hours-vasculitis patients were younger (P=0.004) and tended to have nonfocal stenosis.

Conclusions—In our cohort of young patients with minimal risk factors, atherosclerosis seems to be an uncommon pathology of middle cerebral artery stenosis. HR-MRI aids us to make a more reliable diagnosis.

Key Words: atherosclerosis ■ dissection ■ middle cerebral artery ■ Moyamoya disease

Cerebral artery atherosclerosis, a major cause of ischemic stroke, can be divided into intracranial atherosclerosis (ICAS) and extracranial atherosclerosis. ICAS is more common in Asians than in Caucasians. Previous studies have addressed the differences in risk factors between ICAS and extracranial atherosclerosis to provide a possible explanation for the racial difference, but the results have been inconsistent; reports that hypertension, diabetes mellitus, and metabolic syndrome are more closely associated with ICAS were not confirmed by other studies. Hence, the reason for racial or individual differences in the location of cerebral atherosclerosis remains unclear.

One of the reasons for the inconsistent results may be an incorrect diagnosis; methods commonly used for the diagnosis of ICAS include computed tomography angiography, magnetic resonance angiography, or conventional angiography. These imaging modalities have limitations in that they can examine only the luminal stenosis without providing information regarding the vascular wall pathology. Therefore, nonatherosclerotic etiologies such as Moyamoya disease (MMD), dissection, and vasculitis may have been erroneously included in the category of ICAS, especially in young patients without significant atherosclerotic risk factors.

Currently, high-resolution magnetic resonance imaging (HR-MRI) enables us to assess the vessel wall pathology. Characterization of atherosclerotic plaques and other pathologies affecting the intracranial artery have been investigated using HR-MRI. The aim of the present study was to investigate the etiologies of unilateral middle cerebral artery (MCA) steno-occlusive disease in young adult patients with minimal atherosclerotic risk factors using HR-MRI.
Methods

Patients
We prospectively enrolled patients who visited the Asan Medical Center, Seoul, Korea, between March 2011 and December 2013 with unilateral MCA disease (≥50% stenosis or occlusion) because of presumptive MCA atherosclerosis. Included were patients who (1) were ≤55 years old and (2) had no or minimal (≤1) atherosclerotic risk factors (eg, hypertension, diabetes mellitus, dyslipidemia, and current cigarette smoking). We excluded patients whose diagnosis was

Figure 1. Characteristic features of high-resolution magnetic resonance imaging (HR-MRI) in patients with presumptive atherosclerosis and Moyamoya disease (MMD). A and B, HR-Athero. 3D TOF-MRA shows focal stenosis of the right middle cerebral artery (MCA; arrow). Proton density HR-MRI reveals eccentric wall thickening (arrowheads) on the antero-basal portion of the stenotic lesion, which is considered to be a plaque. C and D, HR-MMD. 3D TOF-MRA shows focal stenosis of the right MCA (arrow). Proton density HR-MRI shows a collapsed vessel lumen (arrow) with well-developed basal collaterals (arrowheads) in sagittal (upper image) and axial (lower image) sections. MRA indicates magnetic resonance angiography.

Figure 2. Characteristic features of high-resolution magnetic resonance imaging (HR-MRI) in patients with dissection and vasculitis. A and B, HR-Dissection. 3D TOF-MRA shows segmental stenosis of the right middle cerebral artery (MCA; arrow). Proton density-weighted HR-MRI reveals a dissecting flap with pseudolumen formation (arrowheads) on the basal portion of the stenotic lesion. C and D, HR-Vasculitis. 3D TOF-MRA shows multifocal stenosis of the left MCA (arrow). Post-enhanced proton density-weighted HR-MRI indicates a concentric stenosis with diffuse circumferential enhancement (arrowheads). MRA indicates magnetic resonance angiography.
Intracranial Stenosis and High-Resolution MRI

Table 1. Comparison of Clinical Variables Between HR-Athero and HR-Nonathero Patients

<table>
<thead>
<tr>
<th>Variables</th>
<th>HR-Athero (N= 26)</th>
<th>HR-Nonathero (N=69)</th>
<th>P Value</th>
</tr>
</thead>
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<tr>
<td>Age, y</td>
<td>43.6±6.7</td>
<td>40.4±10.0</td>
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<tr>
<td>Male</td>
<td>18 (69.2)</td>
<td>25 (36.2)</td>
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</tr>
<tr>
<td>Risk factors</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No/Yes</td>
<td>18 (69.2)</td>
<td>45 (65.2)</td>
<td>0.712</td>
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<tr>
<td>Hypertension</td>
<td>8 (30.8)</td>
<td>11 (15.9)</td>
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<tr>
<td>Diabetes mellitus</td>
<td>3 (11.5)</td>
<td>4 (5.8)</td>
<td>0.340</td>
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<tr>
<td>Hyperlipidemia</td>
<td>8 (30.8)</td>
<td>25 (36.2)</td>
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<tr>
<td>Current smoking</td>
<td>13 (50.0)</td>
<td>17 (24.6)</td>
<td>0.018</td>
</tr>
<tr>
<td>F.Hx of stroke</td>
<td>8 (30.8)</td>
<td>21 (30.4)</td>
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</tr>
<tr>
<td>Headache</td>
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<td></td>
<td>0.265</td>
</tr>
<tr>
<td>New</td>
<td>3 (11.5)</td>
<td>16 (23.2)</td>
<td>0.185</td>
</tr>
<tr>
<td>Chronic</td>
<td>2 (7.7)</td>
<td>10 (14.5)</td>
<td></td>
</tr>
<tr>
<td>Degree of stenosis</td>
<td></td>
<td></td>
<td>0.125</td>
</tr>
<tr>
<td>Stenosis</td>
<td>22 (84.6)</td>
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<td>Occlusion</td>
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<td>23 (33.3)</td>
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<td>Pattern of stenosis</td>
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<td></td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Focal</td>
<td>17 (65.4)</td>
<td>19 (27.5)</td>
<td>0.086</td>
</tr>
<tr>
<td>Segmental</td>
<td>5 (19.2)</td>
<td>21 (30.4)</td>
<td>0.031</td>
</tr>
<tr>
<td>Total</td>
<td>4 (15.4)</td>
<td>29 (42.0)</td>
<td>0.016</td>
</tr>
<tr>
<td>Ipsilesional distal ICA</td>
<td>8 (30.8)</td>
<td>15 (21.7)</td>
<td>0.086</td>
</tr>
<tr>
<td>Contralesional MCA</td>
<td>2 (7.7)</td>
<td>17 (24.6)</td>
<td>0.031</td>
</tr>
<tr>
<td>A1 portion of ACA</td>
<td></td>
<td></td>
<td>0.016</td>
</tr>
<tr>
<td>Ipsilesional A1</td>
<td>1 (3.8)</td>
<td>14 (20.3)</td>
<td>0.086</td>
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<td>Both A1</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Variables are presented as the mean±standard deviation (SD) or as percentages (%). ACA indicates anterior cerebral artery; F.Hx of stroke, family history of stroke; HR-athero, presumptive atherosclerosis by high-resolution magnetic resonance imaging (HR-MRI); HR-MMD, presumptive Moyamoya disease by HR-MRI; HR-nonathero, presumptive nonatherosclerosis by HR-MRI; HR-vasculitis, presumptive vasculitis by HR-MRI; ICA, internal carotid artery; and MCA, middle cerebral artery.

*P value was calculated from the comparison among HR-athero, HR-MMD, HR-dissection, and HR-vasculitis groups.
†P<0.008 for the comparison between HR-athero and HR-vasculitis groups.
‡P<0.008 for the comparison between HR-athero and HR-MMD groups.

Imaging

MR imaging was performed using the Achieva 3.0-T HR-MRI scanner (Philips Healthcare, Eindhoven, The Netherlands). Three-dimensional time-of-flight magnetic resonance angiography, T1-weighted, T2-weighted, proton density–weighted, and contrast-enhanced proton density images were obtained. The parameters of the imaging sequences were as follows: T1-weighted (repetition time/echo time, 600/12 ms; slice thickness, 1.5 mm; 512×512 matrix); T2-weighted (repetition time/echo time, 3000/80 ms; slice thickness, 1.5 mm; 512×512 matrix); and proton density (repetition time/echo time, 1000/20 ms; field of view, 200×200 mm; matrix size, 720×720 matrix; slice thickness, 1 mm; interslice gap, 0.5 mm; average, 1). Sagittal images were obtained perpendicular to the M1 segment of the relevant MCA. Post-enhanced T1-weighted enhanced image were taken using gadolinium unless contraindicated.

Image Analysis

The HR-MRI findings were reviewed and interpreted by consensus between a stroke neurologist (S.H. Ahn) and a neuro-radiologist (D.H. Lee), both of whom were blind to the findings of the initial MRI and clinical characteristics of the patients.

A presumptive diagnosis was made based on HR-MRI according to previous reports,15–17 that is, (1) atherosclerotic disease based on HR-MRI findings (HR-athero): an HR-MRI showing eccentric, irregular wall thickening; gadolinium enhancement of the plaque may be present reflecting plaque instability (Figure 1A and 1B); (2) MMD based on HR-MRI findings (HR-MMD): an HR-MRI showing extensive development of basal collateral vessels and concentric narrowing of the vessel lumen without plaque or eccentric wall thickening (Figure 1C and 1D); (3) dissection based on HR-MRI findings (HR-Dissection):
an HR-MRI showing a dissecting flap or eccentric wall thickening associated with T1 bright wall components representing an intramural hematoma (Figure 2A and 2B); and (4) vasculitis based on HR-MRI findings (HR-Vasculitis): an HR-MRI showing smooth circumferential concentric wall thickening with diffuse gadolinium enhancement of the inflamed wall (Figure 2C and 2D). The pattern of stenosis was classified into focal (≤1/3 of M1 segment), segmental (≤2/3 of M1 segment), multifocal, or total involvement.

### Clinical Assessment
Demographic features and risk factors were recorded including, hypertension (defined as receiving medication for hypertension or blood pressure >140/90 mm Hg on repeated measurements), diabetes mellitus (defined as receiving medication for diabetes mellitus, fasting blood sugar ≥126 mg/dL, or 2-hour postprandial blood sugar ≥200 mg/dL), hyperlipidemia (defined as receiving medication for hypercholesterolemia or an overnight fasting cholesterol level >200 mg/dL or low-density lipoprotein ≥130 mg/dL), and cigarette smoking (a current smoker or a patient who quit smoking <6 months prior).

### Statistical Analysis
The Fisher exact test or χ² test was performed to assess the categorical variables. Differences in continuous variables were evaluated using the Student’s t test. In addition, the comparison among 4 groups was also performed by analysis of variance for continuous variables. A 2-tailed P value of <0.05 was considered statistically significant. For multiple testing, a significance level was considered as 0.008 (=0.05/6) by Bonferroni correction. Statistical analyses were conducted using SPSS for Windows (version 17.0, IBM SPSS, Chicago, IL).

### Results

#### Patient Characteristics
A total of 95 patients (43 men) were enrolled. The mean age±SD was 41.3±9.3 years. The vascular risk factors included hypertension (n=19, 20.0%), diabetes mellitus (n=7, 7.4%), hyperlipidemia (n=33, 34.7%), cigarette smoking (n=30, 31.6%), and a family history of stroke (n=29, 30.5%).

#### Segregation of Patients With HR-Athero Versus Other Diseases
HR-athero was diagnosed in 26/95 (27.4%) patients, whereas 69 patients revealed findings of nonatherosclerotic diseases (HR-nonathero; Table 1). The HR-athero group was more often associated with male (18/26 [69.2%] versus 25/69 [36.2%]; P=0.004), smoking (13/26 [50.0%] versus 17/69 [24.6%]; P=0.018), and focal stenosis (17/26 [65.4%] versus 19/69 [27.5%]; P=0.003) than the HR-nonathero group.

#### Comparison Between HR-Athero and Subgroups of HR-Nonathero
Of the 69 HR-nonathero patients, there were 29 in the HR-MMD group, 22 in the HR-dissection group, and 18 in the HR-vasculitis group (Table 1). Compared with the HR-athero patients, the HR-MMD patients were more often female (P<0.001) and more often had occlusive lesions (P=0.001) and focal stenosis (P<0.001). The HR-dissection patients tended to have hypertension less often (P=0.020). The HR-vasculitis patients were younger (P=0.004) and tended to have nonfocal stenosis (P=0.018). The comparison among the 4 groups was also presented in Table 1.
significant differences in clinical characteristics between the patients who underwent cerebral angiography and those who did not, except for the age (Table I in the online-only Data Supplement). The presumptive diagnoses based on the cerebral angiography and the HR-MRI was identical in the majority of patients, but 13 cases showed a discrepancy (Table 2). Among the 18 HR-MMD patients, 4 patients had presumptive atherosclerosis or MMD by cerebral angiography caused by suspicious development of Moyamoya vessels. Among the 15 HR-dissection patients, 6 patients had presumptive atherosclerosis by cerebral angiography. Among the 12 HR-vasculitis patients, 2 had suspected MMD, whereas one had presumed atherosclerosis by conventional angiography.

### Discussion

Using HR-MRI, we examined the vessel wall status in young adult patients with unilateral MCA disease who had minimal risk factors. HR-MRI including black-blood precontrast and postcontrast T1-weighted sequences with fat suppression image can delineate the arterial wall from the lumen and the surrounding perivascular structures, and postcontrast T1-weighted sequences can be used to identify the contrast enhancement of the arterial wall. 12

We found that only 26 of the 95 (27.4%) patients showed HR-MRI findings compatible with atherosclerosis. Other nonatherosclerotic findings included HR-MMD (29 patients), HR-dissection (22 patients), and HR-vasculitis (18 patients).

The HR-athero patients were more often male and smokers. Cigarette smoking is an important risk factor for cerebral infarction in young adults. 19 The male dominance in the HR-athero group may in part be because of the different smoking prevalence between males and female. There also is a tendency for HR-athero patients to be older and more often have vascular risk factors. Therefore, the presence of risk factors, especially smoking, suggests atherosclerotic pathology even in young patients.

We found that HR-MMD is the most often encountered finding among patients without HR-athero. Although MMD is characterized by bilateral distal internal carotid artery or MCA occlusions with well-developed basal collaterals, atypical cases, such as those with unilateral steno-occlusive disease, are occasionally encountered. 20 Moreover, in the early stage, patients may present with focal MCA stenosis without sufficient development of basal collaterals. 21 HR-MRI may aid us in the diagnosis of MMD by revealing features, such as concentric narrowing of the vessel without wall thickening, and the fine meshwork of basal collateral vessels (Figure 1C and 2D). 17 In our series, there were 4 patients with equivocal diagnosis (atherosclerosis or MMD; cases 1–4 in Table 2) who were eventually considered an MMD after an HR-MRI examination.

MMD is more prevalent in women, 22 and previous reports on Asian patients have shown that ICAS is more closely associated with a female sex and younger age than extracranial atherosclerosis. 23,24 Considering the high prevalence of
HR-MMD among nonatherosclerotic MCA disease in our cohort, we suspect that these epidemiological results may, at least in part, be because of an erroneous inclusion of MMD in the ICAS group, especially in Asian patients. We suggest that HR-MRI is useful in the diagnosis of MMD, particularly in atypical cases.

HR-Dissection has been found to be another common finding in our cohort. Cervicocerebral artery dissection accounts for 1% to 2% of all ischemic strokes and is one of the major causes of stroke in young patients. Intracranial dissection is less frequent (12.5%–13.4%) and seems to occur in relatively younger patients than those with extracranial dissections. However, the frequency of intracranial dissections may have been underestimated because of diagnostic difficulties. HR-MRI may provide supporting evidence of dissection, such as a dissecting flap, mural hematoma, or thrombus (Figure 2A and 2B). In our current analysis, 6 of the HR-dissection patients (cases 5–10 in Table 2) were initially diagnosed as having presumptive atherosclerosis even after cerebral angiography (Figure 3). HR-MRI seems to be especially useful in identifying the chronic stage of dissection because in this stage many patients show nonspecific findings, such as segmental stenosis or occlusion without revealing pathognomonic findings (eg, an intimal flap, false lumen, or pseudoaneurysm).

HR-vasculitis in our study was associated with young age and tended to have nonspecific stenotic lesions than HR-athero. Previous reports have shown that inflammatory conditions are associated with concentric, circumferential wall thickening and enhancement (Figure 2C and 2D). However, the laboratory test results supporting vasculitis (eg, lupus anticoagulant, anticardiolipin antibody, rheumatoid factor, antinuclear antibody, antids-DNA antibody, beta-2-GPI antibody, and an antithyroid antibody test), which were done in 12 of our 18 HR-vasculitis patients, were generally negative; only 2 patients showed a positive antinuclear antibody test and 1 was positive for anti-TPO antibody. This is probably related with our exclusion of typical vasculitis patients (eg, clear clinical and laboratory evidence of infection). Although our HR-vasculitis patients did not show characteristic findings suggesting other pathologies (eg, eccentric wall thickening or concentric narrowing, etc), vessel walls in patients with atherosclerosis or MMD may also be enhanced. Furthermore, vasculitis may show variable enhancement pattern of the vessel wall (eg, eccentric wall enhancement) or even diminishing enhancement pattern depending on the inflammatory status. Therefore, HR-MRI may not be highly specific for the diagnosis of vasculitis. Further studies are required to elucidate the correct pathology in patients revealing HR-MRI findings suggestive of vasculitis, despite the lack of clinical and laboratory evidence of vasculitis.

Our study had limitations. First, there was a lack of histopathologic correlations with which to compare the HR-MRI findings. With difficulty in obtaining pathological findings, identification of susceptibility gene, such as RNF213, may further consolidate the diagnosis of MMD. The gene tests were available only recently in our center, and we were able to identify only 3 patients who showed positivity. Further studies on MMD patients are required that used both HR-MRI and gene tests. Second, our enrolled patients were all Koreans. Because certain diseases, such as MMD, are more prevalent in Asians, the proportion of nonatherosclerotic disease in our series may not be generalizable. Despite these limitations, our data show that nonatherosclerotic intracranial MCA stenosis is prevalent in young patients with minimal risk factors who are initially considered to have presumptive ICAS with conventional magnetic resonance angiography. Contamination with these nonatherosclerotic intracranial diseases may have distorted the results of previous epidemiological studies of ICAS. More importantly, it seems that at least some patients with intracranial stenosis are erroneously diagnosed and treated. HR-MRI allows us to examine the vessel wall and aid the diagnosis of atherosclerosis versus other etiologies, including MMD, dissection, and vasculitis.

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Disclosures
None.

References

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**SUPPLEMENTAL MATERIAL**

**Supplemental Table I. Characteristics of the patients who underwent cerebral angiography (+) and those who did not (-)**

<table>
<thead>
<tr>
<th>Variables</th>
<th>Cerebral angiography (+)</th>
<th>Cerebral angiography (-)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yrs)*</td>
<td>39.6 ± 9.7</td>
<td>43.8 ± 8.2</td>
<td>0.031</td>
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<tr>
<td>Male</td>
<td>22 (39.3)</td>
<td>21 (53.8)</td>
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<td>HR-Athero</td>
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<td>HR-MMD</td>
<td>18 (32.1)</td>
<td>11 (28.2)</td>
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<td>HR-Dissection</td>
<td>15 (26.8)</td>
<td>7 (17.9)</td>
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<tr>
<td>HR-Vasculitis</td>
<td>12 (21.4)</td>
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<td>Risk factors</td>
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<tr>
<td>No/Yes</td>
<td>35 (62.5)</td>
<td>28 (71.8)</td>
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<td>Hypertension</td>
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<td>Diabetes mellitus</td>
<td>4 (7.1)</td>
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<td>Hyperlipidemia</td>
<td>18 (32.1)</td>
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<td>0.525</td>
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<tr>
<td>Current smoking</td>
<td>17 (30.3)</td>
<td>13 (33.3)</td>
<td>0.759</td>
</tr>
<tr>
<td>Family history of stroke</td>
<td>17 (30.4)</td>
<td>12 (30.8)</td>
<td>0.966</td>
</tr>
</tbody>
</table>

Variables are presented as the mean ± standard deviation (SD)* or as the number (percentage)  
HR-Athero, presumptive atherosclerosis by HR-MRI; HR-MMD, presumptive Moyamoya disease by HR-MRI; HR-Dissection, presumptive dissection by HR-MRI; HR-Vasculitis, presumptive vasculitis by HR-MRI.
脳血管造影および高解像度磁気共鳴画像（HR-MRI）の両者で所見が異なる患者の分析結果。A, B: 脳血管造影では、左側近位M1部（矢印）に限局性狭窄が認められ、最初はアテローム性動脈硬化症と考えられていた。C, D: プロトン密度強調HR-MRIは磁気濃度の異常を示しており、動脈硬化に陥った血管内膜の変性（矢頭）と合致している。MRA: 核磁気共鳴血管撮影。