Characteristics of Childhood Arterial Ischemic Stroke With Normal MR Angiography

Pinki Munot, MD, MRCPCH; Dawn Saunders, MD, FRCR; Vijeya Ganesan, MD, MRCP

Background and Purpose—The purposes of this study were to describe clinical and radiological characteristics of children with arterial ischemic stroke and normal MRA to compare them with children with arterial ischemic stroke and abnormal MRA.

Methods—We conducted a retrospective review of clinical records and imaging.

Results—Forty children with arterial ischemic stroke and normal MRA were identified (24 male; median age, 55 months). MRA had been acquired <24 hours of symptom onset in 4, at 24 to 48 hours in 10, 48 to 96 hours in 10, 4 to 7 days in 10, and >1 week in 6 children (median, 4 days). Ten of 40 had prior diagnoses (5 cardiac, 5 malignancies). Other risk factors were identified in 30 (1 in 17 and >1 in 13; prothrombotic abnormalities in 14, prior Varicella in 7, anemia in 7, minor trauma in 4). Infarction was confined to the lenticulostriate branches of the middle cerebral artery in 21 of 40. Two patients had further clinical events, both with new infarcts; 28 patients were reimaged and MRA remained normal in all. Although similar in terms of age and gender to those with abnormal MRA, children with normal MRA were significantly more likely to have at least 1 RF (P = 0.012). Those with abnormal MRA were significantly more likely to have multiple territory infarcts (P < 0.001), but lesion topography was otherwise not predictive of abnormal MRA (P = 0.45). Abnormal MRA was significantly associated with clinical recurrence (P < 0.001).

Conclusions—Children with arterial ischemic stroke and normal MRA are not a distinct demographic group but are more likely to have single-territory lesions and have nonvascular risk factors. The stroke mechanism in children with normal MRA remains unclear. 

Key Words: arterial infarction ■ cerebrovascular ■ children ■ pediatric ■ stroke

Annual ischemic stroke (AIS) causes significant mortality and morbidity in childhood. Most affected children have nonatheromatous abnormalities of the intracranial or cervical circulation on MR angiography (MRA), which predict prognosis. It is not clear whether those with normal MRA are a distinct group. Our aims are to describe the characteristics of such a group, to compare them with a historical group of children with AIS and abnormal MRA, and to describe follow-up imaging findings.

Methods
AIS was defined as an acute focal neurological syndrome attributable to cerebral infarction in an arterial distribution. This was a retrospective study of children (1 month to 16 years) seen at our hospital with AIS and normal cervical and intracranial MRA between 2000 and 2009. Children with sickle cell disease were excluded. The “cerebrovascular disease group” comprised 82 children with AIS and abnormal initial cerebrovascular imaging, described in detail previously.

Clinical details were extracted from charts. All had been investigated for AIS risk factors (RFs) according to departmental guidelines. Our standard AIS MRI protocol includes axial T2- and diffusion-weighted imaging, 2-dimensional time-of-flight MRA from the aortic arch to the circle of Willis, and axial T1-weighted imaging with fat suppression through the neck. The first parenchymal and vascular imaging studies were reviewed. Infarct topography was described as follows: middle cerebral artery (MCA) territory (subdivided into lenticulostriate, partial MCA, and complete MCA), internal carotid artery territory, posterior circulation territory, and multiple arterial territories. Outcome was assessed on mortality, stroke recurrence, and neurological deficit. Follow-up parenchymal and vascular imaging were reviewed, where available, to identify any new areas of infarction and to re-evaluate the cerebral and cervical circulation.

Statistical Analysis
Data were analyzed using logistic regression to identify factors associated with MRA status (normal versus abnormal). Gender, age, known prior diagnosis, number of risk factors (0, 1, or >1), and presence or absence of cardiac abnormality were entered into univariable analyses with the intention of entering significant predictors into a multivariate model. χ² analysis was used to compare rates of recurrence in patients with and without arteriopathy.

Results
The study group comprised 40 children (24 boys; Table 1) with a median age of 4.6 years (range, 2 months to 15.6 years).
years). Thirty-six (90%) presented with acute hemiparesis (see Table 2 for presenting symptoms). Two-dimensional time-of-flight MRA of the circle of Willis was normal in all. Cervical arterial MRA was done in 38 children and was normal in all. MRA had been undertaken <24 hours of symptom onset in 4, at 24 to 48 hours in 10, 48 to 96 hours in 10, 4 to 7 days in 10, and >1 week in 6 children (median, 4 days; range, 6 hours to 5 months).

AIS Risk Factors
Ten children had prior diagnoses; 5 had an underlying malignancy and 5 had cardiac pathology (1 viral myocarditis, 2 dilated cardiomyopathy, and 2 complex congenital heart disease). Other AIS RFs were identified in 30 (1 RF in 17 and 2 RFs in 13; prothrombotic abnormalities in 14, prior Varicella

Table 2. Presenting Symptoms in 40 Children With AIS Without Arteriopathy on MRA

<table>
<thead>
<tr>
<th>Symptom</th>
<th>No. of Patients</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Unilateral weakness</td>
<td>36</td>
<td>90%</td>
</tr>
<tr>
<td>Difficulty speech</td>
<td>5</td>
<td>12.5%</td>
</tr>
<tr>
<td>Dizziness</td>
<td>2</td>
<td>5%</td>
</tr>
<tr>
<td>Seizure</td>
<td>2</td>
<td>5%</td>
</tr>
<tr>
<td>Headache</td>
<td>4</td>
<td>10%</td>
</tr>
<tr>
<td>Decrease in level of consciousness</td>
<td>3</td>
<td>7.5%</td>
</tr>
<tr>
<td>Loss of balance or coordination</td>
<td>1</td>
<td>2.5%</td>
</tr>
<tr>
<td>Acute vision problems</td>
<td>2</td>
<td>5%</td>
</tr>
<tr>
<td>Vomiting</td>
<td>2</td>
<td>5%</td>
</tr>
<tr>
<td>Fever</td>
<td>3</td>
<td>7.5%</td>
</tr>
<tr>
<td>New-onset dystonia</td>
<td>1</td>
<td>2.5%</td>
</tr>
</tbody>
</table>

Outcome
Mean duration of follow-up was 22 months (range, 0.1 to 84 months). Two children died and 5 were lost to follow-up. Two children had a clinical recurrence 6 and 8 months after the index AIS (1 with acute myeloid leukemia, 1 with no RF and no patent foramen ovale) with new areas of infarction but vascular imaging remained normal. Of 28 follow-up scans in 24 children after a median of 12 months (range, 4 to 24 months), only these 2 showed new infarcts. MRA remained normal in all.

Cerebrovascular Disease Group
The cerebrovascular disease group comprised 82 children (median age, 6 years; range, 1 month to 16 years; Table 1) whose clinical and radiological data were collected, analyzed, and described as part of a previous study. All had abnormal MRA, specifically large artery occlusion in 23, large artery stenosis in 23, moyamoya in 23, arteritis in 4, and dissection in 9 children, respectively. Thirty-six had no identified RFs for AIS, 37 had 1 RF, and 9 had >1 RF. Seventy-six of 82 had an echocardiogram. Twenty-nine had recurrent events a median of 2 years after initial AIS (range, 1 day to 12 years). Eleven of them had evidence of reinfarction on reimaging.

Comparison of Patients With Normal and Abnormal MRA
There was no significant difference in gender ($\chi^2$, $P=0.4$) or age ($t$ test, $P=0.6$) between the 2 groups (Table 3). In univariable logistic regression analysis, patients with normal MRA were significantly more likely to have at least 1 identified AIS risk factor ($P=0.012$; Table 2). Children with abnormal MRA were significantly more likely to have multiple rather than single territory infarcts ($\chi^2$, $P<0.001$); however, more detailed subcategorization of lesion topography, as shown in Table 1, was not predictive of presence or absence of arteriopathy (logistic regression, $P=0.45$; Table 1). None of the other variables was significantly predictive. Patients with abnormal MRA were significantly more likely to have had a clinical recurrence than those with normal MRA ($\chi^2$, $P<0.001$).

Discussion
Although children with AIS and normal MRA do not differ demographically from those with arteriopathy on MRA, they...
are significantly more likely to have identified nonvascular AIS RFs and to have single, as opposed to multiple, territory infarcts. Abnormal MRA is associated with a higher risk of recurrence, as has been previously observed.\textsuperscript{7,9}

This study has several potential weaknesses. Our patients were only studied with MRA, not an intraluminal vascular imaging technique, and arteriopathy might have been underdetected. We have referred to them as patients with normal MRA rather than patients without arteriopathy because we recognize that the 2 may not be equivalent. However, the most common site of arteriopathy in childhood AIS is in the large intracranial arteries, in particular the proximal MCA and terminal internal carotid artery,\textsuperscript{4,6} where time-of-flight MRA usually overestimates pathology.\textsuperscript{10} Children with normal MRA may have had embolic disease with early recanalization before the MRA; data on the interval between presentation and imaging were not available for the cerebrovascular disease group but was often delayed in those in whom no arteriopathy was identified. However, a potential embolic source was only identified in a minority. Finally, it is also possible that the location of arteriopathy was in small arteries beyond the resolution of MRA, but this seems unlikely given the infarct topography observed. Thus, it seems likely that at least a proportion of patients in the normal MRA group had no cerebral arteriopathy.

The comparison of the study group with a historical cohort could also be criticized. However, both were derived from the same hospital, had brain MRI (addressing the issue of lesion topography), and the vast majority had echocardiography. We acknowledge that it is possible that in the time since this group was seen, new RFs for AIS have been recognized or would come to light with investigation; this must be acknowledged as a potential explanation for the finding that nonvascular risk factors, especially prothrombotic risk factors, were more common in children with normal MRA.

The most commonly observed cerebrovascular abnormality in children with AIS is stenosis of the terminal internal carotid artery or proximal MCA. Sebire et al proposed this should be termed “transient cerebral arteriopathy”\textsuperscript{11} and described cases with initially normal arterial imaging who subsequently developed characteristic abnormalities. None of our patients had cerebrovascular abnormalities on follow-up imaging and do not fulfill diagnostic criteria for transient cerebral arteriopathy.\textsuperscript{11}

An outstanding question is the optimal modality for vascular imaging in childhood AIS. MRI identifies cerebral ischemia earlier, enables differentiation from other pathologies, and better delineates the extent of injury. The opportunity to incorporate vascular imaging is attractive, especially if serial imaging may be needed. Catheter cerebral angiography has an ongoing role in the investigation of childhood AIS but is now largely confined to cases of diagnostic uncertainty,\textsuperscript{12} those where the posterior circulation is poorly seen, cases of possible vasculitis,\textsuperscript{13} and perioperative imaging of moyamoya. Cerebral angiography should also be considered in children with normal MRA who have recurrent events to exclude small vessel disease.

In conclusion, children with AIS and normal MRA do not form a distinct demographic group; they are more likely to have single territory lesions and to have nonvascular RFs for AIS. These data support comprehensive vascular imaging and investigation of all children with AIS, especially because they confirm the prognostic importance of arteriopathy. The exact stroke mechanism in patients with normal MRA remains unclear.

Disclosures

None.

References

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