Unilateral Intracranial Arteriopathy in Pediatric Stroke
Course, Outcome, and Prediction of Reversible Arteriopathy

Je Young Yeon, MD; Hyung Jin Shin, MD; Ho Jun Seol, MD; Jong-Soo Kim, MD; Seung-Chyul Hong, MD

Background and Purpose—The nonprogressive, often reversible, unilateral arteriopathy known as transient (focal) cerebral arteriopathy has become a leading cause of childhood arterial ischemic stroke. However, it is not a well-recognized arteriopathy in East Asian countries where moyamoya disease is prevalent.

Methods—We retrospectively reviewed 74 children and adolescents (<18 years) with arterial ischemic stroke and intracranial arteriopathy to identify 29 patients with unilateral large-artery arteriopathy mainly in the anterior circulation. Among them, 25 patients who fulfilled the following inclusion criteria were analyzed to determine the angiographic course and outcome: (1) repeated vascular imaging at least twice and (2) absence of thrombotic disorders or cardiac diseases.

Results—The course of unilateral arteriopathy was classified as reversible in 17 patients (68%), progressive in 5 (20%), and stable in 3 (12%). Nine of the 17 patients with reversible arteriopathy exhibited initial worsening of the arteriopathy mostly within 1 month, but the worsened arteriopathy began to improve within 3 months and continued to improve even after a few years. Two of these 9 patients experienced stroke progression at 6 days. Of the variables analyzed, infarction involving the basal ganglia (15 of 17) and arterial beading on angiography performed within 2 weeks (10 of 12) were associated with reversible arteriopathy. Involvement of the ipsilateral posterior cerebral artery was rare (1 of 17).

Conclusions—The possibility of reversible arteriopathy should be suspected in children and adolescents presenting with arterial ischemic stroke and unilateral arteriopathy.

Key Words: moyamoya disease ■ pediatrics ■ stroke

The nonprogressive, often reversible, unilateral arteriopathy known as transient cerebral arteriopathy (TCA) or focal cerebral arteriopathy has been recognized as a leading cause of childhood arterial ischemic stroke (AIS).1,2 The definition of TCA includes 2 primary criteria: (1) unilateral steno-occlusion involving the distal part of internal carotid artery and the initial segments and branches of anterior and middle cerebral artery (MCA) and (2) occasional worsening of the arteriopathy <3 months but nonprogression >6 months after AIS.3 The pathophysiology of TCA is still poorly understood, but it is thought to be a self-limited inflammatory process, generally extending for 1 to 3 months.1

Focal cerebral arteriopathy is a newly coined label for arteriopathy with no specific diagnosis.2 Because the diagnosis of TCA depends on the reversible or stable course of arteriopathy on repeated vascular imaging, unilateral focal cerebral arteriopathy has been suggested at baseline to describe unilateral arteriopathy that may be eventually diagnosed as TCA.4 However, TCA or focal cerebral arteriopathy is not a well-recognized arteriopathy in East Asian countries where moyamoya disease is the principal cause of childhood AIS. In the initial stage, TCA may not be distinguished from unilateral moyamoya or other progressive arteriopathies such as vasculitis.1,3

Materials and Methods

We retrospectively reviewed 74 children and adolescents (6 months to 17 years) who presented with AIS and intracranial arteriopathy to identify 29 patients with unilateral large-artery arteriopathy mainly in the anterior circulation. The Samsung Medical Center institutional review board approved this study and waived the need for consent from patients. All patients underwent 3-dimensional time-of-flight magnetic resonance angiography (MRA) at the time of AIS (within 2 days, including cervical arteries) and standard blood and cardiac investigations (eg, thrombotic disorder profiles and echocardiography with contrast). Among the 29 patients, 25 patients who fulfilled the following inclusion criteria comprised the study population: (1) repeated vascular imaging at least twice and (2) absence of thrombotic disorders or cardiac diseases including patent foramen ovale.

The mean age was 9.1 years, and 12 patients were men. Five patients had a recent history of upper respiratory infection. Two other patients had experienced varicella zoster infection 3 and 9 months before AIS, respectively. The ischemic lesions on MRI were simply classified into 2 patterns based on the presence or absence of basal ganglia involvement. The involvement of the internal carotid artery,
MCA, anterior cerebral artery, and posterior cerebral artery was assessed on the initial MRA. Digital subtraction angiography (DSA) was available in 22 patients and was usually performed within 2 weeks. In addition to the location and type of arteriopathy, the presence of abnormal vascular networks (basal collaterals [moyamoya vessels] or transdural collaterals) or arterial beading (alternating short segments of stenosis) was investigated on the initial DSA.1

MRA with MRI was repeated if the patient experienced any neurological deterioration. Recurrent stroke was defined as any neurological deterioration >2 weeks after the index stroke, accompanied by new areas of infarction. Even if the patient remained asymptomatic, MRA with MRI was repeated at 2 to 6 months and every 6 to 12 months thereafter to assess the evolution of arteriopathy. Follow-up DSA was generally considered in patients aged >10 years (under local anesthesia) to confirm the evolution of arteriopathy. The mean number of repeated vascular imaging was 4.7 during the mean radiological follow-up of 37 months.

The evolution of arteriopathy was determined as improved, worsened, or unchanged by comparing the findings (apparent luminal diameter as well as the longitudinal extent of arteriopathy and distal filling) of identical angiographic techniques (MRA or DSA). Then, the overall course of unilateral arteriopathy was determined as reversible, progressive, or stable.1,4 Reversible unilateral arteriopathy was defined as an arteriopathy showing any improvement including normalization. Initial (transient) worsening within 6 months was also considered to be indicative of reversible arteriopathy if the subsequent imaging demonstrated any improvement. Progressive unilateral arteriopathy was characterized by continued worsening of arteriopathy beyond 6 months or progression to bilateral arteriopathy. In cases with worsening of arterial lesions within the first 6 months but no change thereafter, the arteriopathy was classified as stable.

Results

The overall course of unilateral arteriopathy was classified as reversible in 17 of the 25 patients (68%). Of these 17 patients, improvement shown by MRA was confirmed by repeated DSA in 6 and by subsequent MRA (further improvement thereafter) in additional 6. Nine patients exhibited initial worsening of the arteriopathy that almost always occurred within 1 month (Figure 1). Two of these 9 patients experienced clinical worsening at 6 days with an additional infarction (stroke progression). However, the worsened arteriopathy began to improve within 3 months and continued to improve even after a few years (Figure 2). Eventually, the arteriopathy nearly normalized in 12 of the 17 patients. One patient underwent revascularization surgery because the reversible arteriopathy was mistaken for unilateral moyamoya. Recurrent stroke developed in only 1 patient 14 months later, but there was no apparent change in the improving but residual MCA stenosis.

Five patients (20%) had progressive unilateral arteriopathy that demonstrated initial worsening within 4 to 6 months and further worsening thereafter (n=2) or worsening after

Figure 1. Time course of reversible unilateral arteriopathy during the first year of stroke. Gray bars indicate the radiological follow-up period (days) of each case (in the order of age at onset). The changes of arteriopathy at the time of repeated vascular imaging are shown with black arrows (worsening), white arrows (improvement), and gray circles (no interval change).
6 months (n=3). Of these 5 patients, worsening shown by MRA was confirmed by repeated DSA in 3 (Figure I in the online-only Data Supplement) and by subsequent MRA (further worsening thereafter) in the other 2. Four patients underwent revascularization surgery. But, one of them developed recurrent stroke and another 2 experienced transient ischemic attacks after revascularization surgery. Only 3 of the 25 patients (12%) were regarded as having stable unilateral arteriopathy that remained unchanged (n=1) or stable (stabilized) after initial worsening (n=2).

Of the variables analyzed, infarction involving the basal ganglia and beading on the initial DSA were associated with reversible arteriopathy (Table). However, ipsilateral posterior cerebral artery involvement and abnormal vascular networks were predictive of progressive arteriopathy. Male sex and only MCA involvement were more commonly observed in reversible arteriopathy, but this difference did not reach statistical significance.

**Discussion**

The prevalence of reversible unilateral arteriopathy in the present study (68%, 17 of 25) was comparable with that in the European multicenter study (63%, 50 of 79). But, unlike the high prevalence of stable arteriopathy in the above study (30%), only 12% of our patients were considered to have stable arteriopathy probably because of a longer radiological follow-up and more frequent vascular imaging. There is limited information on the predictors of reversible arteriopathy in the literature. Our study showed that patients with reversible arteriopathy almost always present with basal ganglia infarction (15 of 17) with (n=6) or without (n=9) MCA involvement.

### Table. Comparison Between Reversible and Progressive Unilateral Arteriopathy

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Reversible Arteriopathy (n=17)</th>
<th>Progressive Arteriopathy (n=5)</th>
<th>P Value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age &lt;9 y</td>
<td>8/17, 47%</td>
<td>3/5, 60%</td>
<td>1.000</td>
</tr>
<tr>
<td>Men</td>
<td>11/17, 65%</td>
<td>1/5, 20%</td>
<td>0.135</td>
</tr>
<tr>
<td>Right hemisphere infarction</td>
<td>7/17, 41%</td>
<td>1/5, 20%</td>
<td>0.613</td>
</tr>
<tr>
<td>Infarction involving the basal ganglia</td>
<td>15/17, 88%</td>
<td>1/5, 20%</td>
<td>0.009</td>
</tr>
<tr>
<td>Only MCA involvement†</td>
<td>8/17, 47%</td>
<td>0/5, 0%</td>
<td>0.115</td>
</tr>
<tr>
<td>Ipsilateral PCA involvement‡</td>
<td>1/17, 6%</td>
<td>3/5, 60%</td>
<td>0.024</td>
</tr>
<tr>
<td>Beading‡</td>
<td>10/12, 83%</td>
<td>0/5, 0%</td>
<td>0.003</td>
</tr>
<tr>
<td>Abnormal vascular networks‡</td>
<td>0/12, 0%</td>
<td>3/5, 60%</td>
<td>0.015</td>
</tr>
</tbody>
</table>

MCA indicates middle cerebral artery; and PCA, posterior cerebral artery.

*Derived from Fisher exact test.

†On the initial magnetic resonance angiography within 2 days.

‡On the initial digital subtraction angiography within 2 wk (available in only 17 patients).
territory cortical infarction. Ipsilateral posterior cerebral artery involvement was rare (1 of 17; Figure II in the online-only Data Supplement).

Another interesting finding of reversible unilateral arteriopathy is arterial beading (Figure III in the online-only Data Supplement). When the initial DSA was performed within 2 weeks, beading was observed in 10 of 12 patients with reversible arteriopathy and 0 of 5 patients with progressive arteriopathy. The 3 patients, in whom DSA was performed >1 to 2 months after AIS, did not show beading despite having reversible arteriopathy. Although beading may be considered to be nonspecific, it has been usually associated with reversible conditions and diseases such as TCA and reversible cerebral vasoconstriction syndrome. The likely mechanism of beading would be arterial wall inflammation of unknown causes (presumed viral infection in some cases) inducing transient multifocal vasoconstriction.

Despite the small case number, the present study reports the course and outcome of unilateral arteriopathy among East Asian patients with AIS for the first time. Considering the typical time course of initial worsening and improvement, repeated vascular imaging at 1, 3, and 6 to 12 months would be necessary to differentiate reversible arteriopathy clearly from progressive arteriopathy. However, stroke progression may occur in the initial worsening stage, and there are potentially treatable causes of progressive arteriopathy. The early identification of patients likely to have reversible or progressive arteriopathy would ensure proper management and guide further research for secondary stroke prevention.

Disclosures
None.

References
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SUPPLEMENTAL MATERIAL

Unilateral Intracranial Arteriopathy in Pediatric Stroke: Course, Outcome, and Prediction of Reversible Arteriopathy
Supplementary Figure I

(Figure legend: An example of progressive unilateral arteriopathy in a 13-year-old girl. Note the borderzone infarction associated with distal ICA stenosis. Abnormal vascular networks (moyamoya vessels) are not visualized on the initial DSA. Ipsilateral ACA progression was suggested by MRA at 6 months and confirmed by DSA at 1.5 years. Additionally, ipsilateral MCA progression is shown on the follow-up DSA. MRA performed at 4 years shows further MCA progression and well-formed surgical collaterals.)
Supplementary Figure II

(Figure legend: A rare example of reversible unilateral arteriopathy with ipsilateral PCA involvement. This 15-year-old female patient presented with acute infarction involving the thalamus, the basal ganglia, the temporo-parietal lobe, and the occipital lobe. Note the mild left PCA stenosis as well as the left MCA/ICA stenosis on the initial MRA. The initial DSA confirmed the left PCA stenosis and also revealed MCA/ICA beading which persisted on follow-up DSA at 19 days. Similar to other reversible arteriopathies, this PCA stenosis as well as the MCA/ICA stenosis worsened within 1 month but improved after 1 year. Involvement of the basilar artery or vertebral artery was not observed. We assumed that PCA involvement might be attributable to inflammation extension through the posterior communicating artery. This assumption would be supported by concurrent thalamic infarction and non-visualization of the posterior communicating artery on follow-up vascular imaging (Note the posterior communicating artery on the initial MRA). The rarity of PCA involvement would be best explained by the more proximal origin and variations (e.g. hypoplasia or aplasia) of the posterior communicating artery.)
Supplementary Figure III

(Figure legend: Typical examples of arterial beading on the initial DSA performed within 2 weeks)