Chickenpox and Stroke in Childhood
A Study of Frequency and Causation

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Background and Purpose—The purpose of this study was to determine whether infection with varicella is causal for arterial ischemic stroke (AIS) in children.

Methods—First, a prospective cohort study was conducted in young children (aged 6 months to 10 years) with AIS at 2 institutions (cohort study). The presence of varicella infection <12 months before AIS was determined and compared with the published frequency of varicella infection in the healthy pediatric population. The clinical and radiographic features of AIS were compared between the varicella and nonvaricella study cohorts. Second, a literature search of varicella-associated AIS was conducted, and the clinical and radiographic features were compared with the study nonvaricella cohort.

Results—In the cohort study, 22 (31%) of 70 consecutive children with AIS had a varicella infection in the preceding year compared with 9% in the healthy population. Children in the varicella cohort were more likely to have basal ganglia infarcts (P<0.001), abnormal cerebral vascular imaging (P<0.05), and recurrent AIS or transient ischemic attacks (P<0.05) than those in the nonvaricella cohort. The pooled literature analysis of 51 cases of varicella-associated AIS showed similar findings to the varicella cohort.

Conclusion—In young children with AIS, there is a 3-fold increase in preceding varicella infection compared with published population rates, and varicella-associated AIS accounts for nearly one third of childhood AIS. Varicella-associated AIS has characteristic features, including a 2-fold increase in recurrent AIS and transient ischemic attacks. Varicella is an important risk factor for childhood AIS. (Stroke. 2001;32:1257-1262.)

Key Words: chickenpox ■ child ■ etiology ■ stroke

Arterial ischemic stroke (AIS) during childhood, although relatively rare, occurs and frequently causes significant long-term morbidity.1,2 The etiologies of AIS during childhood are multifactorial and differ from those during adulthood, in which atherosclerotic disease is the most common etiology. Varicella has been identified as one potential risk factor for AIS during childhood. However, the evidence consists of case reports and small retrospective case series.3–20 The presence of a preceding varicella infection has not been systematically surveyed in series of children with AIS, nor have the clinical and radiographic features been compared between varicella-associated AIS and other forms of childhood AIS. The objective of the current study was to establish whether varicella is likely causal for childhood AIS. Two approaches were used, a prospective cohort study and a pooled analysis of the literature.
appropriate) gave written consent for the study. The Institutional Review Boards of both participating centers approved the study protocol.

Definition of Arterial Ischemic Stroke
The definition of AIS was a focal neurological deficit of acute onset, and a CT scan or MRI of the brain showing a lesion characteristic of focal arterial infarct in a vascular territory consistent with the neurological presentation.

Clinical Features
Clinical information was obtained by the study neurologists (D.M., R.C., B.M., G.de.V.) during the acute hospitalization or in subsequent clinics 3 to 6 months after AIS. A previously reported Pediatric Stroke Outcome Measure (PSOM) was used that consisted of a standardized structured questionnaire, radiographic AIS classification, and neurological examination.1 Data were supplemented by comprehensive standardized health-record reviews of all cases. Information obtained included age at event, sex, neurological signs and symptoms at presentation with AIS, risk factors, and antithrombotic therapy. The presence and timing of the varicella infection were established by asking the parents the following questions: “Has your child had chickenpox?” and if the response was yes, “When?” The number of days, months, and years that varicella infection preceded the AIS was documented. The rate of varicella infection in the children with AIS was compared with published rates of varicella in healthy children obtained by community survey and parental reporting.21 Laboratory investigations for metabolic disorders, prothrombotic conditions, and vasculitis were performed. Cardiac echocardiography was performed in all patients.

Radiographic Features
All patients underwent CT, MRI, MR angiography (MRA), or conventional angiography. The study neuroradiologist (S.L.), who was unaware of the clinical history, reviewed all original radiographic films for children in the varicella cohort and a randomly selected patients (31%) with varicella in the 12 months preceding their initial AIS formed the varicella cohort, and the remaining 48 children composed the nonvaricella cohort. The clinical and radiographic features are summarized for both the varicella and nonvaricella cohorts in Table 1.

Clinical Features
The mean interval from varicella infection to AIS in the varicella cohort was 5.2 months (range 1 to 11 months; Figure). There was no seasonal pattern to the frequency of AIS in the varicella or nonvaricella cohort. There were no significant differences between the varicella and nonvaricella cohorts in Table 1. Children in the varicella cohort were less likely than children in the nonvaricella cohort to have additional risk factors (12% versus 27%, respectively). The additional risk factors included: congenital heart disease (5% versus 23%), migraines (10% versus 10%), other vasculopathies (0% versus 21%), presence of anticardiolipin antibody (33% versus 36%), and other (1% versus 14%). Children in the varicella cohort were more likely than children in the nonvaricella cohort to receive antithrombotic therapy (82% versus 65%, respectively), which included aspirin (58% versus 48%), heparin (18% versus 16%), and coumadin (6% versus 1%).

Radiographic Features
All patients had CT or MRI to confirm the diagnosis of AIS. All children in the varicella cohort and 28 children in the nonvaricella cohort underwent vascular imaging. In the varicella cohort, 20 children had MRA, 19 conventional angiography, and 17 had both. Review of 20% of the institutional films for the nonvaricella cohort by the study neuroradiologist showed 100% agreement with the institutional radiology reports for the presence or absence of basal ganglia infarction, anterior circulation infarction, and cerebral artery abnormalities. Therefore, information from the institutional radiology reports was used for the remaining nonvaricella cohort patients.

Children in the varicella cohort were significantly more likely than children in the nonvaricella cohort to have an infarct located in the basal ganglia (P<0.001), infarct(s) limited to the anterior circulation (P<0.05), and a large-
vessel stenosis ($P<0.05$). The vascular abnormalities in the varicella cohort consisted nearly exclusively of areas of stenosis (20 of 22) in the proximal portion of the major cerebral arteries.

**Neurological Outcome**

The final neurological outcome assessments for the study cohorts were performed 3 months to 5.8 years (mean 2.1 years) after the AIS. Neurological outcomes in the varicella cohort were normal in 7 (32%), with the remaining 15 (68%) having neurological deficits graded as mild (10), moderate (2), and severe (3). All 3 children with severe deficits developed progressive hemidystonia beginning several months after the AIS. Neurological outcomes in the 48 children in the nonvaricella cohort were normal in 16 (33%), while the remaining 32 had neurological deficits graded as mild (9), moderate (12), and severe (11). The neurological outcomes did not differ significantly in the 2 groups.

**Recurrence**

Recurrent AIS occurred in 10 (45%) children in the varicella cohort compared with 8 (20%) children in the nonvaricella cohort ($P<0.05$). All 5 children with recurrent infarcts also had recurrent TIAs. Recurrences were associated with stenosis on the MRA or angiogram in 9 children and were multiple (up to 7 episodes) in 8 of the 10 children. Four children were receiving aspirin therapy at the time of recurrence.

**Pooled Literature Analyses**

Since 1980, 18 case series with a total of 57 cases of children with varicella-associated AIS have been published. Of the 57 cases, there were 51 cases (designated literature-varicella group) in which the varicella occurred <12 months before the AIS, and adequate information on age, interval from varicella to infarct, and infarct location were provided. The clinical and radiographic features are summarized for the literature-varicella group in Table 2.

**Clinical Features**

The mean interval from varicella infection to AIS in the literature-varicella group was 2.6 months, with a range from 0.2 to 12 months. Similar to the varicella cohort, there were no significant differences between the literature-varicella group and nonvaricella cohort for age and sex, but a clinical presentation with hemiparesis was significantly more likely in the literature-varicella group compared with the nonvaricella cohort ($P<0.001$).

**Radiographic Features**

Radiographic studies included CT scanning that was performed in all but 2 cases, conventional angiography in 33, MRI in 17, and MRA in 1. Similar to the varicella cohort, children in the literature-varicella group were significantly more likely than children in the nonvaricella cohort to have infarcts located in the basal ganglia (Table 2; 50 of 51 cases, $P<0.001$). Of the 33 children in the literature-varicella group that underwent vascular imaging, 5 were normal and the remainder had large-vessel stenosis ($P<0.05$).

**Neurological Outcome**

Information on neurological outcome was available in 40 children, of whom 13 (32%) were described as normal and 27 (68%) had neurological deficits. The deficits were graded as mild in 8, moderate in 9, and severe in 10. There were no significant differences in neurological outcome between the literature-varicella group and nonvaricella cohort.

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**Table 1. Comparison of Varicella Stroke and Nonvaricella Stroke Cohorts**

<table>
<thead>
<tr>
<th>Patient Characteristics</th>
<th>Varicella Cohort</th>
<th>Nonvaricella Cohort</th>
<th>$P$ (2-sided)</th>
<th>OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>No.</td>
<td>22</td>
<td>48</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age, mean (SD), y</td>
<td>4 (2.4)</td>
<td>5 (3.1)</td>
<td>0.49</td>
<td>...</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>15</td>
<td>31</td>
<td>0.44</td>
<td>1.6 (0.5–4.6)</td>
</tr>
<tr>
<td>Female</td>
<td>7</td>
<td>17</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Clinical</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hemiparesis</td>
<td>22</td>
<td>38</td>
<td>0.02*</td>
<td>12.2 (0.68–219.7)</td>
</tr>
<tr>
<td>Seizures</td>
<td>3</td>
<td>17/44</td>
<td>0.05</td>
<td>0.2 (0.1–0.9)</td>
</tr>
<tr>
<td>Radiographic</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Basal ganglia infarct</td>
<td>22</td>
<td>18</td>
<td>&lt;0.001*</td>
<td>74 (4.2–1298.1)</td>
</tr>
<tr>
<td>Multiple infarcts</td>
<td>7</td>
<td>17</td>
<td>1.00</td>
<td>0.9 (0.2–2.5)</td>
</tr>
<tr>
<td>Anterior circulation</td>
<td>20</td>
<td>32</td>
<td>0.04*</td>
<td>5.0 (1.0–24.1)</td>
</tr>
<tr>
<td>Large-vessel stenosis</td>
<td>20</td>
<td>19/31</td>
<td>0.03*</td>
<td>6.3 (1.2–32.1)</td>
</tr>
<tr>
<td>Outcome</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Normal</td>
<td>7</td>
<td>16</td>
<td>1.0</td>
<td>0.9 (0.3–2.7)</td>
</tr>
<tr>
<td>Recurrence</td>
<td>10</td>
<td>8</td>
<td>0.01*</td>
<td>4.1 (1.3–12.9)</td>
</tr>
</tbody>
</table>

*Statistically significant at $P<0.05$. 

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the remainder as having hemiparesis that was graded as mild in 8 or of unspecified severity in 5. These outcomes did not differ from outcomes in the nonvaricella cohort (Table 2; \( P = 1.0 \)).

Recurrence
Information on recurrent TIA or AIS was available in 20 children, of whom 9 (45%) had a recurrence, which represents an increased recurrence rate compared with the nonvaricella cohort \(( P < 0.05 \)).

Discussion
This is the first prospective cohort study to systematically search for varicella as a preceding cause of AIS in children and to differentiate the clinical and radiographic features of varicella-associated AIS from other forms of AIS. Our results show that 31% of consecutive children with AIS have a history of varicella in the preceding year. Children with varicella-associated AIS have an increased frequency of hemiparesis, basal ganglia infarcts, anterior circulation infarcts, and stenosis of proximal portions of major cerebral arteries compared with AIS in children without varicella. Although the association of AIS with varicella does not appear to influence the neurological outcome, the risk of recurrent AIS or TIA is significantly increased.

The age range of children in our study was selected because varicella is difficult to diagnose in children aged <6 months and rare in children aged >10 years. \(^{21}\) The 31% incidence of varicella within the preceding year in our AIS cohort represents a 3-fold increase over the 9% annual incidence of varicella in Canadian children. Among idiopathic AIS, the incidence of varicella-related strokes increases 6-fold (to 50%) compared with population rates. \(^{6}\) Although varicella is an important risk factor for AIS, the absolute risk of varicella-associated AIS is estimated at only 1 in 15 000 children. \(^{5,6,24,25}\) The reasons that such a small percentage of children with varicella experience AIS are not known. Variations in immune susceptibility or in the strain of the varicella-zoster virus may account for differing susceptibilities to varicella-related AIS.

Parental reporting was selected in our study for identification of a recent varicella infection because of previously proven accuracy. \(^{21}\) Other methods that were considered included measuring varicella titers and examination of cerebrospinal fluid. However, the problematic issues with these methods included the inability to provide information on the timing of the infection and poor sensitivity in the case of molecular testing for varicella zoster (VZ) in the cerebrospinal fluid. \(^{26–28}\) Definitive histopathological evidence for the presence of VZ virus in the affected vasculature through postmortem examination was not available, as all children survived.

The clinical and radiographic features of varicella-associated AIS that differed significantly from nonvaricella AIS included hemiparesis, infarction in the basal ganglia and anterior cerebral circulation, and stenosis of proximal portions of major cerebral arteries. The increased frequency of hemiparesis and anterior circulation territory infarcts in varicella-associated AIS reflected the location of all infarcts in the basal ganglia. Case series of childhood basal ganglia strokes have reported frequencies of varicella ranging from 5% to 56%. \(^{10,29}\) In our entire study cohort, 55% of all children with basal ganglia infarcts had varicella. The underreporting of varicella as a risk factor for AIS in children in the literature likely reflects the delay of several months from infection to AIS and failure to specifically obtain a history of varicella. Obtaining a history of varicella is particularly important in children with basal ganglia AIS, even when there are other identified risk factors.

<table>
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<tr>
<th>TABLE 2. Comparison of Literature Varicella Stroke Group and Nonvaricella Stroke Cohort</th>
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<tbody>
<tr>
<td>Patient Characteristics</td>
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<tr>
<td>No.</td>
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<tr>
<td>Normal</td>
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<tr>
<td>Recurrence</td>
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*Statistically significant at \( P < 0.05 \).
The underlying mechanism for varicella causing AIS is not known. Multiple mechanisms for varicella-associated AIS have been suggested. The most plausible mechanism involves intraneuronal migration of the VZ virus from the trigeminal ganglion along the trigeminal nerve to the cerebral arteries. In adults with herpes zoster opthalmicus (HZO) and delayed cerebral infarction, VZ virus is present within the media of the affected large cerebral arteries. The distribution of vascular lesions in varicella-associated AIS in large cerebral arteries is similar and matches the anatomic location and density of trigeminal innervation at the circle of Willis.

The neurological outcome in the varicella cohort was similar to that in the nonvaricella cohort at the time of analyses. However, the emergence of longer-term complications of basal ganglia infarction, especially dystonia, needs to be monitored. The significant increase in recurrent TIA's and AIS in the varicella cohort was unexpected and may influence long-term neurological outcome. The risk of recurrence indicates that more effective antithrombotic strategies need to be developed.

Initial treatment options for varicella-associated AIS include supportive care, antiviral therapy, and anticoagulant therapy. Antiviral therapy has not been reported in children with varicella-associated AIS, and the results of treatment with acyclovir and steroids in adults with HZO are with varicella-associated AIS, and the results of treatment with antiviral therapy. Antiviral therapy has not been reported in children.

The distribution of vascular lesions in varicella-associated AIS includes supportive care, antiviral therapy, and anticoagulant therapy. Antiviral therapy has not been reported in children with varicella-associated AIS, and the results of treatment with acyclovir and steroids in adults with HZO are mixed. However, antiviral and anti-inflammatory therapies may not be indicated in children with varicella-associated AIS, as the survival rate is excellent compared with a mortality of 25% in adults with HZO. Anticoagulant therapy in the initial phases of varicella-associated AIS may be helpful in preventing local extension of the thrombus and embolization.

Primary prevention of varicella-associated AIS by the varicella vaccine is an important consideration, but the impact would likely be modest. A recommendation for varicella immunization for the prevention of childhood AIS cannot be made because the risk/benefit ratio and cost-effectiveness of immunizing 15 000 children to prevent 1 AIS have not been assessed. In contrast, secondary prevention with anticoagulants in children with varicella-associated AIS should be seriously considered. The options include antplatelet agents, warfarin, and low-molecular-weight heparin (LMWH). At this time, long-term therapy with aspirin can be suggested for all children with varicella-associated AIS for secondary prevention. More effective but potentially less safe treatment with warfarin or LMWH should, in general, be reserved for children in whom stroke recurs while on aspirin, until these treatments have been studied in clinical trials.

In summary, our study has shown that there is a strong association between varicella infection and childhood AIS and that there are distinctive clinical and radiographic features of varicella-associated AIS, which include an increased risk of recurrent AIS and TIA. The long-term clinical and radiographic outcomes, as well as the role of antiviral therapy, more effective antithrombotic therapy, and the impact of immunization for varicella on childhood AIS require further study.

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References

In the article by Askalan et al, the authors report a strong association between varicella infection and a particular form of childhood arterial ischemic stroke (AIS). They describe a triad of basal ganglionic infarction in association with an anterior circulation stenotic vasculopathy accompanied in two thirds of patients by recurrent stroke or transient ischemic attacks. Although mortality is low, the morbidity can be high, with the more neurologically devastated cases proceeding to hemidystonia (3 of 31).

The authors are to be congratulated on their study design, which might not have been possible without the development of the Canadian pediatric stroke database (deVeber et al). It is a 3-pronged approach that consists of a prospective cohort study of children with AIS, a review of the reported demographics of varicella in the community, and a metaanalysis of the literature.

This article should raise awareness of pediatric stroke in the medical community. The incidence is currently underestimated and unrecognized. The occurrence of childhood stroke is likely to increase in the future, with technical advances such as fetal surgery and extracorporeal membrane oxygenation allowing children who might otherwise not have survived to enter the community. To use the old aphorism, “children are not little adults,” and this is nowhere more true than in pediatric stroke, where the etiology of cerebrovascular accident is predominantly hematoatic or cardiovascular and not atherosclerotic, as in the adult population. This point leads on to the need for clinical trials of anticoagulant and antithrombotic therapies in children. There are few enough controlled trials in adults, and they cannot be assumed to extrapolate to the pediatric population.

At our institution, we have developed a multidisciplinary approach to the diagnosis and management of pediatric AIS. At the time of admission, an unenhanced CT scan is performed to rule out the presence of blood and, following a thorough neurological examination, a complete blood work-up is performed to include protein S activity, antithrombin III activity, protein C activity, and factor V Leiden and prothrombin gene mutations, in addition to CBC, platelet count, ESR, ANA, APLA, lactate, pyruvate and homocysteine levels, PT, and PTT. MRI and MR angiography are carried out in addition to diffusion-weighted imaging (DWI).

The sensitivity of DWI is such that we have detected changes of ischemic damage within 20 minutes of a cerebrovascular event in a child. Transesophageal echocardiography form part of the routine workup to establish an etiology. Conventional angiography is reserved for those cases in which no cause has been found or to better demonstrate a suspicious area noted, for example, on MRA.

In the case of varicella-associated AIS in children, it is interesting to speculate whether antiviral agents might offer some protection in addition to anticoagulant therapy. The future impact of vaccination programs may further reduce the incidence of varicella vasculopathy, although only time will help us further elucidate the mechanism of stroke in these patients.

Finally, while only 1 in 15,000 cases of varicella may result in AIS, this article raises a bigger question as to how to elevate awareness of the phenomenon of pediatric stroke both within the medical community and among the lay public, for although with chickenpox the mortality may be low, the morbidity is high, and society will continue to pay the cost of a damaged child for many years to come.

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Guest Editor
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