Predictors of Stroke After Transient Ischemic Attack in Children

Laura L. Lehman, MD; Christopher G. Watson, BS; Kush Kapur, PhD; Amy R. Danehy, MD; Michael J. Rivkin, MD

Background and Purpose—Transient ischemic attack (TIA) in children has received far less attention compared with TIA in adults. The risk factors of stroke after TIA in children are relatively unknown. We aimed to determine the percentage of children who have stroke after TIA and the risk factors associated with stroke after TIA.

Methods—We searched the medical records at Boston Children’s Hospital for the year 2010 to find children who were evaluated for TIA to determine associated risk factors of stroke after TIA. We included children who were evaluated in 2009 through 2010 for TIA and had magnetic resonance imaging. We examined follow-up imaging through August 2014 for subsequent stroke. Logistic regression was used to calculate odds ratios for factors in our cohort who are associated with stroke after presentation with TIA.

Results—We identified 63 children who experienced a TIA. The mean time of imaging follow-up was 4.5 years after TIA presentation. Of the 63 children, 10 (16%) developed radiological evidence of ischemic cerebral injury within the follow-up period. Four of the 10 (6%) demonstrated diffusion abnormalities on magnetic resonance imaging at TIA presentation, whereas 8 (13%) had a stroke after their TIA. Arteriopathy, female sex, and autoimmune disorders were significantly associated with stroke after TIA.

Conclusions—In our cohort of children, stroke occurred after TIA at a rate similar to that seen in adults, but the risk factors for stroke after TIA in children are different. (Stroke. 2016;47:00-00. DOI: 10.1161/STROKEAHA.115.009904.)

Key Words: child ■ heart disease ■ ischemic attack, transient ■ risk factor ■ stroke

Transient ischemic attack (TIA) in children has received scant investigation, whereas TIA in adults has been well defined, extensively studied, and is regarded as a critically important sign for determination of need for stroke prophylaxis. Stroke occurs within 3 months of a TIA in 10% to 15% of affected adults.1,2 Recently, Adil et al examined a nationwide inpatient database using International Classification of Diseases Ninth Revision (ICD-9) codes and found that 4% of children admitted with TIA also had a secondary diagnosis of stroke during the same admission. However, TIA remains incompletely described in children, and the proportion of children who will prove to have stroke after TIA presentation remains unknown.

The pathophysiology of stroke in children differs from that in adults. Pediatric stroke risk factors include arteriopathy, thrombophilia, and congenital heart disease.3,4 The pathophysiology of TIA in children has not been examined thoroughly. However, TIA in children has been associated with moyamoya arteriopathy, sickle cell anemia, thrombophilia, congenital heart disease, and intracardiac right to left shunt.3,5 Thus, the pathophysiology of TIA in children may also be different than in adults.

Previously, in adults, TIA has been defined as the sudden onset of focal neurological symptoms that resolve fully within 24 hours.10 However, it is now recognized that despite resolution of symptoms, evidence of cerebral ischemia by neuroimaging can be found in some adult patients. Adults who experience a TIA demonstrate diffusion abnormality consistent with acute ischemia on brain magnetic resonance imaging (MRI) at the time of their symptoms in 28% to 40% of cases.11,12 Those adults with transient neurological symptoms accompanied by diffusion abnormality have a 7% to 12% increased risk of subsequent stroke in the next 7 days, compared with only 0.4% to 1.2% with transient neurological symptoms alone.11,12 Recently, the American Heart Association proposed using a tissue-based definition, which stipulates transient neurological symptoms without neuroradiologic evidence of infarction and would replace the previous time-based definition of focal neurological symptoms that resolve fully within 24 hours.14,15 However, the proportion of...
children who have acute ischemia on brain MRI at the time of their transient neurological symptoms and their risk for subsequent stroke is unknown.

Specific clinical features of adult patients at the time of TIA have been found to predict subsequent stroke in the next 90 days. These comprise diffusion MRI abnormality at the time of TIA, presence of a motor deficit, TIA duration longer than 10 minutes, age >60 years, blood pressure ≥ 140/90, and diabetes mellitus.13,14 Specific clinical features associated with TIA that impart increased risk for subsequent stroke have not been determined in children. Moreover, the extent to which TIA symptoms in children are associated with MRI evidence of new cerebral injury has not been investigated. We present a cohort of 63 children with suspected TIA and relate the clinical and neuroimaging features of these transient neurological episodes. In addition, we examined their clinical outcome with respect to the occurrence of stroke after TIA.

Materials and Methods

Patients
We searched the patient medical record database at Boston Children’s Hospital in the year 2010 with the terms transient ischemic attack or TIA. We identified 820 medical records that contained either search term. A child neurologist (L.L.L.) reviewed all records. TIA was defined as a focal neurological deficit that resolved completely within 24 hours of onset. Because a definition in children has not yet been established, we used a broad definition try to capture as many episodes as possible that might have been TIA. Symptoms were categorized as altered mental status, dizziness, focal motor, focal sensory, language related, or visual. Of the 820 records, we identified 63 patients (7.7%) who had a suspected TIA in 2009 through 2010, were 18 years of age or younger at the time of the TIA, and had a MRI within 3 months of TIA symptoms. Because we searched the medical records for TIA and transient ischemic attack, we obtained duplicate records of patients. We also found multiple patients with the same name as the search word, Tia. Because a large adult congenital heart disease patient population exists at our hospital, many of these patients have had a TIA. However, they were excluded because they were > 18 years. Finally, when an echocardiogram is done in the setting of stroke sometimes, the order includes mention of TIA or stroke. This study was approved by the Boston Children’s Hospital Institutional Review Board.

Data Collection
A neuroradiologist (A.R.D.) blinded to the patient’s clinical presentation and outcome evaluated all neuroimaging. Initial imaging included head computed tomography, computed tomographic angiography, MRI, magnetic resonance angiography, and catheter angiogram. If the patient had additional imaging after the index TIA, the most recent MRI occurring after TIA through August 2014 was also reviewed to determine whether the child had a stroke after TIA presentation.

We collected demographic information and medical features from the patients’ charts including symptoms at presentation. Data on risk factors known to be associated with pediatric stroke, including congenital heart disease, arteriopathy, sickle cell anemia, thrombophilia, and inflammatory/autoimmune disorders, were collected.4-6,17-19

Statistical Analysis
We used logistic regression to calculate odds ratios (ORs) with 95% confidence intervals (CIs) and P values for the estimated parameters to determine which stroke risk factors, presenting symptoms, and medical factors were associated with stroke after TIA presentation. We also tested the association of these medical factors with stroke after TIA presentation using Fisher exact test and have placed these values in the online-only Data Supplement as we have a small sample size. We used the false discovery rate procedure with testing bounds of 0.05 and 0.10 to control for multiple comparisons.20,21 Statistical significance was defined as P value < 0.05.

Results
Sample Characteristics
Sixty-three patients met inclusion criteria. Our cohort comprised 28 women (44%) and had the following racial composition: 51 whites (81%), 4 black (6%), 1 Asian (2%), 6 other (10%), and 1 unidentified (2%). Age at time of TIA ranged from 2 to 18 years (median, 13; mean, 12).

Clinical Characteristics
Duration of the initial TIA symptoms ranged from 30 seconds to 24 hours. Recurrent TIAs occurred in 38 patients (60%). Presenting symptoms were several: motor symptoms in 50 (79%), lateralized sensory symptoms in 34 (54%), aphasia in 29 (46%), visual symptoms in 21 (33%), altered mental status in 14 (22%), and dizziness in 6 (10%). Furthermore, 53 children (84%) had ≥ 2 symptoms. Headache accompanied TIA symptoms in 32 children (51%). Of these, 22 (69%) had previous history of headache. Migraine had been previously diagnosed in only 6 (10%). A total of 34 (54%) had childhood stroke risk factors. Of these, 7 (11%) had new risk factors discovered at time of TIA.

Risk factors for childhood stroke included arteriopathy (n=12; 19%), history of prior stroke (n=9; 14%), congenital heart disease (n=6; 10%), recent illness (n=5; 8%), autoimmune disorder (n=4; 6%), and sickle cell disease (n=2; 3%).

Neuroimaging
Of 63 children, 52 (83%) had diffusion-weighted imaging, 39 (62%) of whom had imaging within 10 days of TIA presentation. The mean imaging follow-up period was 4.5 (+0.54) years after TIA presentation. Arteriopathy was present in 12 of the children (19%), 9 of whom had moyamoya (75%), whereas 2 had central nervous system vasculitis (25%). Of the 12 children with arteriopathy, all had magnetic resonance angiographic imaging, and 11 had cerebral catheter angiography. In the cohort, stroke preceded presentation with TIA in 9 (14%), 7 (78%) of whom also had arteriopathy. Four of the 12 children with arteriopathy (33%) were diagnosed with arteriopathy at time of TIA.

After clinical presentation with TIA, 10 of the 63 patients (16%) developed radiological evidence of ischemic cerebral injury. Interestingly, 4 (6%) of these children had diffusion abnormalities on MRI at the time of the TIA (Figure 1). Furthermore, 8 (13%) demonstrated MRI evidence of cerebral ischemic injury on follow-up MRI, not seen on MRI done at time of TIA. Of the 10 with radiological evidence of cerebral injury, 2 (20%) had both diffusion changes at time of TIA, presence of a motor deficit, TIA duration longer than 10 minutes, age >60 years, blood pressure ≥ 140/90, and diabetes mellitus.
children who had a subsequent stroke, 3 (27%) had >1 stroke after TIA (Figure 2).

**Relationship of TIA With Stroke**

Children with TIA but no subsequent stroke tended to be older than those who had stroke after TIA (mean age, 12.1 [SD, 4.2] versus 9.4 [SD, 4.2] years; \( P = 0.092 \)). Although the majority of children in our TIA cohort were males, females were significantly more likely to develop stroke after TIA (OR, 11.3; 95% CI, 1.3–98.7; \( P = 0.028 \)). A demographic comparison between the children who had a TIA and no stroke and children with TIA and subsequent stroke is shown in Table 1.

All 8 children with TIA and subsequent stroke (100%) had at least 1 pediatric stroke risk factor at presentation (Table 2). Such risk factors were found in only 26 of 55 children (47%) with TIA but no subsequent stroke (\( P < 0.006 \)). Furthermore, among these children, a significant association was found between stroke after TIA and cerebral arteriopathy (OR, 24.5; CI, 4.0–149.8; \( P < 0.0005 \)) and presence of autoimmune disorders (OR, 26.5; CI, 3.6–191.6; \( P = 0.001 \)) compared with children who had a TIA and no stroke (Figure 3). History of prior stroke (OR, 4.9; CI, 0.9–25.8; \( P = 0.061 \)) was marginally significant, whereas all other risk factors presented in Table 3 were not significant. We also calculated significance using Fisher exact test with similar results (Table I in the online-only Data Supplement). Among children found to have a diffusion-weighted imaging abnormality at presentation with TIA, cerebral arteriopathy was significantly more likely to be present when compared with children who had a TIA with neither diffusion abnormality nor subsequent stroke (OR, 9.60; CI, 1.11–83.69; \( P = 0.041 \)).

**Discussion**

We identified 63 pediatric cases of suspected TIA at a single, large pediatric hospital center. Each patient presented with acute onset of neurological symptoms that resolved completely within 24 hours. The majority of our patients presented with motor symptoms, consistent with TIA presentation in adults, and many demonstrated \( >1 \) symptom.\(^2\) Of the 63 patients with suspected TIA, nearly 1 in 5 demonstrated

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**Figure 1.** Neuroimaging of a 17-year-old patient who had diffusion abnormalities at time of transient ischemic attack (TIA). Presenting symptoms comprised ataxia, left facial droop, left sided paresthesias, and blurred vision, all of which resolved fully by 6 hours after onset. Risk factors for stroke consisted of oral contraceptive overdose, cigarette smoking, and an autoimmune disorder. A, Cranial computed topography on presentation revealed right thalamic hypodensity. B, Trace diffusion imaging 7 days after symptoms demonstrated evidence of restricted diffusion in right thalamus. C, Fluid-attenuated inversion recovery imaging acquired 7 days after symptoms showed hyperintensity in the right thalamus.

**Figure 2.** Flow diagram with the 63 children who had a transient ischemic attack (TIA) differentiating those with restricted diffusion at time of TIA and those with stroke on follow-up imaging. * indicates 2 of the children had both diffusion-weighted imaging (DWI) changes at time of TIA and a stroke on follow-up imaging. MRI indicates magnetic resonance imaging.

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**Table 1. Demographics of Our Pediatric Cohort of TIA Patients Who Had a Stroke Compared With Those Who Did Not Have a Stroke**

<table>
<thead>
<tr>
<th>Race</th>
<th>TIA, No Stroke, ( n=55 ), n (%)</th>
<th>TIA, With Stroke, ( n=8 ), n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>White</td>
<td>46 (82)</td>
<td>5 (71)</td>
</tr>
<tr>
<td>Black</td>
<td>4 (7)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Asian</td>
<td>0 (0)</td>
<td>1 (14)</td>
</tr>
<tr>
<td>Other</td>
<td>4 (7)</td>
<td>2 (25)</td>
</tr>
<tr>
<td>Unknown</td>
<td>1 (2)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>34 (62)</td>
<td>1 (13)</td>
</tr>
<tr>
<td>Female</td>
<td>21 (39)</td>
<td>7 (88)</td>
</tr>
</tbody>
</table>

TIA indicates transient ischemic attack.
Table 2. Risk Factors in Children With TIA and Subsequent Stroke

<table>
<thead>
<tr>
<th>Pediatric Stroke Risk Factor</th>
<th>No. of Children With Risk Factor, n=8</th>
</tr>
</thead>
<tbody>
<tr>
<td>Moyamoya</td>
<td>5</td>
</tr>
<tr>
<td>Congenital heart disease</td>
<td>2</td>
</tr>
<tr>
<td>Prior stroke</td>
<td>3</td>
</tr>
<tr>
<td>OCP</td>
<td>1</td>
</tr>
<tr>
<td>Autoimmune disorder</td>
<td>4</td>
</tr>
<tr>
<td>Anemia</td>
<td>1</td>
</tr>
<tr>
<td>Perinatal stroke</td>
<td>1</td>
</tr>
<tr>
<td>Trauma</td>
<td>1</td>
</tr>
<tr>
<td>Smoking</td>
<td>1</td>
</tr>
</tbody>
</table>

OCP indicates oral contraceptive pill; and TIA, transient ischemic attack.

evidence of cerebral infarction by neuroimaging. Restricted diffusion was seen in 6% at the time of TIA and 13% demonstrated stroke subsequent to TIA presentation. Presence of arteriopathy significantly correlated with both the presence of restricted diffusion at the time of TIA and the occurrence of stroke after TIA.

Risk factors for stroke after TIA in adults include presentation with motor symptoms, aphasia without motor symptoms, and signal changes consistent with ischemia on diffusion MRI performed at the time of TIA.1,11–13,22 In our pediatric cohort, we did not find a significant association between symptom type and subsequent stroke. Although some of our patients demonstrated diffusion abnormality on MRI at time of TIA, small sample size prevented determination of whether acute diffusion change at time of TIA was associated with increased risk of future stroke in our cohort. Further work in this regard is needed.

In our cohort, 10 patients had ischemic injury on MRI, 8 (13% of cohort) of whom had evidence of ischemic injury at a time subsequent to their presentation with TIA, similar to the rate of occurrence in adults.1,2 Unlike adults, 5 of the 8 demonstrated silent strokes on follow-up imaging. Furthermore, of these 10 patients, 4 had diffusion abnormalities at the time of their TIA. According to the proposed tissue-based definition in adults, these transient neurological events would be classified as strokes. Whether such a tissue-based definition of TIA as proposed for adults is appropriate for children merits further prospective research and consideration.

Identification of TIA and its clinical features in children, especially those features that increase risk of stroke, constitute critically important first steps in the development of treatment strategies designed to prevent the occurrence of stroke after TIA. Cerebrovascular disorders constitute one of the top 10 causes of death in children and are formidable causes of morbidity that is amortized over a child’s entire lifetime.23–24 Pediatric stroke leads to significant motor and cognitive impairment.25–28 Risk factors for arterial ischemic stroke in children include male sex, thrombophilia, sickle cell anemia, arteriopathy, cardiac disease, and inflammatory states.4–6,17–19,29–30

In our pediatric cohort, risk factors significantly associated with stroke after TIA included female sex, autoimmune disorders, and arteriopathy. In addition, history of prior stroke demonstrated a trend toward significance. Girls with a TIA were 11 times more likely to have a subsequent stroke compared with boys, despite the male predominance in both our TIA cohort and pediatric stroke overall.29 In our cohort, history of stroke imparted a 5-fold increased risk of stroke after TIA presentation. Presence of an autoimmune disorder imparted significant increased risk of stroke after TIA. Autoimmune disorders constitute a known risk factor for stroke in both children and adults.31,32 Interestingly, an increased risk of stroke after TIA has been found in adults with systemic lupus erythematosus.

Children who had a TIA and arteriopathy were significantly more likely to have a subsequent stroke than children with TIA and no arteriopathy. Although moyamoya has been associated with TIA in children, arteriopathy has not been associated with stroke after TIA in either adults or children.4 However, arteriopathy has been associated with an increased risk of recurrent stroke in children. A recent study of pediatric patients in California found that children with arterial ischemic stroke and abnormal vascular imaging had a 66% 5-year recurrence rate compared with no recurrence among children with normal vascular imaging.5 Our study extends these findings and suggests that children who present

Figure 3. Neuroimaging of an 11-year-old patient born at 25 weeks of gestation with history of periventricular hemorrhagic infarct in the left hemisphere who had several transient ischemic attacks (TIAs) with complete symptom resolution between repeated episodes of aphasia, left hand weakness, and paresthesias. A, Head computed topography 1 day after initial TIA did not show any signs of new ischemic injury. B, Trace diffusion imaging 2 days after initial TIA demonstrated evidence of restricted diffusion within the right frontal lobe. C, Catheter angiography of the right internal carotid artery demonstrates stenosis of the internal carotid consistent with cerebral arteriopathy involving the supraclinoid internal carotid artery.
with TIA and cerebral arteriopathy are at increased risk for subsequent stroke when compared with children with no arteriopathy.

Although this study is one of the first to examine the risk of stroke after TIA in children, it nonetheless possesses weaknesses that must be addressed. First, our study was retrospective. Second, the timing at which MRI was obtained and the clinical data available varied among patients. Third, our final sample (63) is limited in size, and the CIs tended to be wide in most cases. We used the false discovery rate method to control for multiple comparisons.20,21 Finally, we excluded any patient with TIA symptoms who did not have MRI within 3 months of presentation. Consequently, some patients with true TIA were likely not included. Conversely, to identify as many children with TIA as possible, we with no doubt included children who had complicated migraine or other stroke/TIA mimics but not TIA. However, this difficulty is endemic to the field of pediatric stroke, and its inclusion permits application of our data to a pediatric stroke. Presence of cerebral arteriopathy, autoimmune disorders, and female sex may identify children who are at higher risk for subsequent stroke after TIA. Additional investigation to identify features of pediatric TIA that impart higher risk for stroke is warranted.

Conclusions

In our cohort of 63 children who presented with suspected TIA, as in adults, we found that TIA symptoms may herald stroke. Presence of cerebral arteriopathy, autoimmune disorders, and female sex may identify children who are at higher risk for subsequent stroke after TIA. Additional investigation to identify features of pediatric TIA that impart higher risk for stroke is warranted.

Disclosures

None.

References


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Data Supplement (unedited) at:
http://stroke.ahajournals.org/content/suppl/2015/11/10/STROKEAHA.115.009904.DC1

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Supplemental Material

Table I. Risk factors and clinical presentation in our pediatric cohort comparing patients with TIA and stroke to those with TIA and no stroke using Fisher’s exact test.

<table>
<thead>
<tr>
<th></th>
<th>TIA no stroke</th>
<th>TIA with stroke</th>
<th>p- value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N=55 Number</td>
<td>N=8 Number</td>
<td></td>
</tr>
<tr>
<td></td>
<td>(percent)</td>
<td>(percent)</td>
<td></td>
</tr>
<tr>
<td>Female Sex</td>
<td>21 (38.5%)</td>
<td>7 (87.5%)</td>
<td>0.018</td>
</tr>
<tr>
<td>Arteriopathy</td>
<td>6 (11.0%)</td>
<td>6 (75.0%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Autoimmune Disorder</td>
<td>2 (3.6%)</td>
<td>4 (50%)</td>
<td>0.002</td>
</tr>
<tr>
<td>Prior stroke</td>
<td>6 (10.9%)</td>
<td>3 (37.5%)</td>
<td>0.080</td>
</tr>
<tr>
<td>Recent Illness</td>
<td>3 (5.5%)</td>
<td>2 (25.0%)</td>
<td>0.117</td>
</tr>
<tr>
<td>Motor symptoms</td>
<td>43 (78.2%)</td>
<td>7 (87.5%)</td>
<td>1.000</td>
</tr>
<tr>
<td>Sensory symptoms</td>
<td>25 (45.5%)</td>
<td>5 (62.5%)</td>
<td>0.462</td>
</tr>
<tr>
<td>Aphasia</td>
<td>23 (41.8%)</td>
<td>0 (0%)</td>
<td>0.023</td>
</tr>
<tr>
<td>Ocular</td>
<td>18 (32.7%)</td>
<td>2 (25.0%)</td>
<td>1.000</td>
</tr>
<tr>
<td>Altered mental status</td>
<td>13 (23.6%)</td>
<td>1 (12.5%)</td>
<td>0.671</td>
</tr>
<tr>
<td>Dizziness</td>
<td>4 (7.3%)</td>
<td>2 (25.0%)</td>
<td>0.164</td>
</tr>
<tr>
<td>Headache at presentation</td>
<td>30 (54.5%)</td>
<td>2 (25.0%)</td>
<td>0.148</td>
</tr>
<tr>
<td>Congenital heart disease</td>
<td>5 (9.1%)</td>
<td>1 (12.5%)</td>
<td>0.573</td>
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