Mode of Onset Predicts Etiological Diagnosis of Arterial Ischemic Stroke in Children

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Background and Purpose—In children, early differentiation among various etiologies of arterial ischemic stroke (AIS) is important. Cerebral arteriopathy is a frequently identified cause of childhood stroke. Children with arteriopathies require a different therapeutic approach from children with AIS of nonarteriopathic origin. We aimed to investigate the association between temporal features of the onset of neurological symptoms and stroke etiology in children with AIS.

Methods—From a consecutive cohort of children (6 months to 18 years) with a confirmed diagnosis of AIS at one center, we selected all patients with transient cerebral arteriopathy (n=10), postvaricella angio- pathy (n=20), dissection (n=8), cardio-embolic (n=8), and cryptogenic stroke (n=10). We retrospectively reviewed medical charts for mode of onset and classified the onset as either abrupt, reaching maximum severity of symptoms within 30 minutes, or nonabrupt, including a progressing, stuttering, or recurring course. We compared the mode of onset in patients with known cerebral arteriopathy to those with nonarteriopathic stroke using multivariate logistic regression modeling.

Results—There were no significant differences for age, gender, location of infarction, seizures, and headache between the arteriopathic and nonarteriopathic group. Most children with nonarteriopathic AIS had an abrupt onset (72%), compared with 32% in children with arteriopathic stroke. With nonabrupt onset, the odds of having an arteriopathic etiology was 6.1 (95% CI, 1.6 to 22.8; P=0.007) after correction for possible confounders.

Conclusions—Mode of onset predicts etiological diagnosis of childhood AIS and may guide prioritization of ancillary investigations and choice of treatment. A nonabrupt onset of symptoms is associated with arteriopathic stroke, particularly with presumed inflammatory arteriopathies. (Stroke. 2007;38:298-302.)

Key Words: child ■ embolism ■ intracranial arterial disease ■ ischemic stroke subtypes

Nonatherosclerotic arteriopathies are increasingly acknowledged as the most frequent causes of pediatric arterial ischemic stroke (AIS). A recent cohort study showed that vascular imaging was normal in only 21% of the non-neonates with AIS. The majority of childhood arteriopathies are monophasic and nonprogressive, particularly dissection, transient cerebral arteriopathy of childhood (TCA), and postvaricella arteriopathy (PVA). Children with TCA and PVA typically have unilateral arterial abnormalities of the distal internal carotid artery or proximal middle or anterior cerebral arteries with small vessel lenticulostriate territory infarction. These arterial abnormalities stabilize, improve, or even normalize in time. Definitions for these and other childhood arteriopathies have recently been proposed. Other important causes and risk factors of childhood stroke include cardiac sources of embolism, as well as prothrombotic abnormalities.

Except for the primary prevention of stroke in sickle cell disease, there is no evidence for any form of acute treatment or secondary prevention in children with ischemic stroke. Recent guidelines, however, have proposed diagnostic and management strategies in children with AIS. It is generally advised to perform vascular imaging, including neck arteries and the intracranial cerebral circulation, as well as echocardiography and a prothrombotic laboratory work-up. However, it is often difficult to time and prioritize ancillary investigations. This may depend on the clinical suspicion of the cause of stroke in each individual patient. Although there are areas of nonconsensus for treatment, most children with dissection and cardio-embolic stroke are treated with anticoagulation (low-molecular-weight heparin or warfarin), whereas most children with other arteriopathies and idiopathic strokes are given aspirin.

The prioritization of ancillary investigations and the choice of acute treatment strategies would greatly benefit from clinical factors that could distinguish between the various etiologies of stroke. This study aims to investigate the association between the mode of onset of neurological symptoms, and the...
etiological diagnosis of childhood AIS. In particular, we correlated abrupt and nonabrupt modes of onset with arteriopathic and nonarteriopathic etiologies for AIS.

Patients and Methods

This study is a retrospective analysis of a prospectively enrolled consecutive cohort of children aged 6 months to 18 years that were evaluated for AIS at the Hospital for Sick Children, Toronto, Canada, for the period extending from January 1995 to December 2000. Inclusion of cases required that the criteria for 4 specific etiological stroke categories as defined here be fulfilled. The study subjects were identified from the Canadian Pediatric Ischemic Stroke Registry, Toronto site. AIS was defined as focal neurological deficits caused by cerebral ischemia, with an infarct in one or more of the territories of the cerebral arteries on cerebral imaging. Patients with only transient ischemic attacks (TIAs) and normal MRI were excluded from the study. Children younger than 6 months of age and patients who showed new neurological symptoms within 72 hours after a cardiac procedure were excluded because their mode of stroke onset is often difficult to determine. Children with moyamoya and diffuse isolated angitis of the central nervous system were also excluded because ischemic strokes are frequently subclinical and the mode of onset is often not evident.

For this study, the four categories of AIS etiologies included were: (1) TCA and PVA; (2) dissection; (3) cardio-embolic stroke; and (4) cryptogenic stroke. Children with TCA had anterior circulation stroke and vascular imaging, performed within 3 months after stroke, revealed unilateral vascular disease, characterized by focal or segmental stenosis or occlusion, affecting the supraclinoid internal carotid artery and/or proximal segments of the anterior cerebral artery or middle cerebral artery. Follow-up vascular imaging, performed at least 6 months after stroke, showed no progression of arterial lesions. Although in some patients initial worsening of arterial abnormalities within the first months may occur, arterial disease eventually stabilizes or improves. Patients with systemic or isolated small vessel central nervous system vasculitis, sickle cell disease, bilateral vascular abnormalities, or predominating small vessel pathology on angiography were excluded. PVA was diagnosed when first-ever anterior circulation AIS was preceded by varicella infection within 12 months, with no other causes for stroke. The diagnosis is supported when vascular imaging reveals identical pathological diagnosis of dissection; (2) MR imaging, angiography, or conventional angiography findings suggestive of dissection, including: bright crescent sign, presence of an intimal flap, double lumen, pseudo aneurysm, and segmental narrowing or occlusion of a vertebral artery at either C1–C2 or C2–C3; and (3) segmental narrowing or occlusion of a cervical artery with a history of preceding head or neck trauma within 2 weeks of presentation.

Data Collection

The medical charts were retrospectively reviewed by 2 of the study child neurologists (K.B. and M.R.). First, the etiological diagnosis and localization of infarct (anterior or posterior circulation) from the Registry database was validated. Second, the mode of onset was abstracted from notes made at admission by the physician on call and the consulting neurology resident, stroke fellow, or child neurologist. In addition, the presence of seizures and headache was noted when occurring during the 4 weeks preceding the day of admission, because we anticipated that inflammatory arteriopathies and dissection may cause headache several days to weeks before cerebral infarction.

This study had approval of the Institution’s Research Ethics Board.

Definition of Subgroups for Mode of Onset

We defined the following modes of onset of neurological deficits:

**Abrupt**

Patients presented with a single episode that started abruptly, reaching maximum severity of deficits within 30 minutes after onset. This group also included children that had fixed neurological deficits of maximum severity on awakening.

**Nonabrupt**

This group included children with progressing, stuttering, recurring, and unclear but not abrupt modes of onset.

**Progressing**

During a single episode, neurological symptoms gradually or smoothly progressed, reaching maximum severity >30 minutes after onset.

**Stuttering**

The course of presenting neurological symptoms was fluctuating, or waxing and waning. The child did not return to normal in between.

**Recurring**

These patients had recurrent episodes of transient neurological deficits before the index stroke but completely returned to normal in between these episodes.

**Unclear But Not Abrupt**

The evolution of symptoms could not be accurately assessed because children went to bed with mild deficits and woke up with severe symptoms, hampering the differentiation between progressive, stuttering, or recurring.

Statistical Analysis

Group differences between patients with arteriopathic and nonarteriopathic AIS were compared using Mann Whitney U test for continuous variables and χ² or Fisher’s exact test for categorical variables. For estimating the association between mode of onset (abrupt versus nonabrupt) and stroke etiology (arteriopathy versus nonarteriopathy), we used logistic regression modeling. First, we modeled etiology (dependent) and onset (independent). Second, we used similar models to adjust for possibly confounding variables (age and localization of infarct in anterior or posterior cerebral circulation). Associations are expressed as odds ratios (OR) with corresponding 95% confidence intervals (CI) and probability values. Analyses were performed with SPSS-12. Statistical significance was considered reached when 95% CIs did not include 1 and \( P < 0.05 \).

Results

Between January 1995 and December 2000, 98 patients, aged 6 months to 18 years, with confirmed AIS were identified from the Canadian Pediatric Ischemic Stroke Registry who were evaluated at the Hospital for Sick Children. Of these 98 children, 56 children met the study inclusion criteria of whom 38 had AIS secondary to specific arteriopathy and 18 were included in the nonarteriopathy subgroup. Of the 38 children...
with arteriopathy, 30 had a presumed inflammatory arteriopathy (10 TCA, 20 PVA), and 8 were identified with dissection (6 extracranial, 2 intracranial). In the 18 children with nonarteriopathic etiology, 8 had cardioembolic AIS and 10 had cryptogenic AIS with normal vascular imaging.

Of the 42 children from the cohort who were not included in this study, 21 experienced another arteriopathy (10 moyamoya, 2 arteriopathy in sickle cell disease, 3 small vessel vasculitis, 2 arteriopathies related to Varicella-Zoster Virus infection but not fulfilling the criteria for PVA, 1 related to HIV infection, 3 other), 17 had a cardioembolic procedure-related stroke, and 4 patients did not undergo vascular imaging, so arteriopathy could not be excluded. Patient characteristics of the 56 patients entered in this study are given in Table 1.

There was a male preponderance (59%). Headache and seizures accompanied the onset of stroke in 45% and 16%, respectively. No significant differences were found for age, gender, localization of AIS, and the occurrence of seizures and headaches, between the arteriopathy and nonarteriopathic stroke group.

Modes of onset for each of the subcategories of stroke etiologies are presented in Table 2. In 55% of patients in the total cohort, the mode of onset was nonabrupt. The majority of children with nonarteriopathic stroke (cardioembolic and cryptogenic) had an abrupt onset (72%), whereas most children with arteriopathic stroke revealed a nonabrupt onset (68%). The association between mode of onset and stroke etiology was highly statistically significant; results of logistic regression showed that with a nonabrupt onset there was a 5.6-times higher chance of arteriopathic stroke than with an abrupt onset (OR, 5.6; 95% CI, 1.6 to 19.4; \(P=0.007\)). When adjusted for age and localization of AIS as possible confounders, using multivariate logistic regression, the OR was 6.1 (95% CI, 1.6 to 22.8; \(P=0.007\)) The mode of onset had considerable discriminatory power (area under receiver operating characteristics curve=0.70; 95% CI, 0.55 to 0.85; \(P=0.015\)).

Interestingly, a stuttering (ie, fluctuating, waxing, and waning) course of symptoms was never seen in children with cardioembolic stroke or stroke with normal vascular imaging, but relatively frequently in inflammatory arteriopathy. In addition, all anterior circulation dissections had an abrupt onset, whereas the 3 children with posterior circulation dissection had a nonabrupt tempo of onset. Patients with a stroke onset that was classified as recurring experienced from 1 to 6 TIAs before the day of admission, with a duration of 1 minute to 12 hours, and a time interval of 5 hours to 3 weeks before admission. The exact timing of the occurrence of infarction in relation to the onset of TIAs and the time of stroke diagnosis could not be determined retrospectively in these patients. The duration of the time course between first symptoms and maximum severity in children whose mode of onset was classified as progressive, varied from 2 hours to 3 months.

### Discussion

We studied the clinical presentation of 56 children with arterial ischemic stroke and found, for the first time to our knowledge, that the mode of onset of neurological symptoms strongly correlates with the underlying cause of stroke. The mode of onset is nonabrupt in the majority (68%) of children with arteriopathic stroke, whereas most children (72%) with stroke attributable to a nonarteriopathic cause have an abrupt start of symptoms.

A limitation of this study is the determination of mode of onset based on retrospective chart review, which may have hampered an accurate distinction between abrupt onset with maximum severity being reached within 30 minutes after onset, and gradual progression during a time interval of >30

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<td>No. of patients</td>
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<tr>
<td>Mean age, y</td>
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<td>Gender, M/F</td>
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<td>Localization AIS, ant/post</td>
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<td>Seizures</td>
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<td>Headache</td>
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AIS indicates arterial ischemic stroke; ant/post, anterior vs posterior circulation; PVA, postvaricella arteriopathy; TCA, transient cerebral arteriopathy.

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<th>TABLE 2. Mode of Onset in Subtypes of Stroke Etiologies</th>
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<td>Mode of Onset</td>
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<tr>
<td>Stroke etiology</td>
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<tr>
<td>Cardioembolic, n=8</td>
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<tr>
<td>Cryptogenic, n=10</td>
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<tr>
<td>Total nonarteriopathy, n=18</td>
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<td>Total Arteriopathy, n=38</td>
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<td>TCA/PVA, n=30</td>
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minutes. However, in all patients in whom mode of onset was classified as progressive, symptoms increased over >2 hours. Because the association between mode of onset and stroke etiology was determined in a selected group of children with specific and well-defined stroke etiologies, the results of this study cannot be automatically generalized to the total population of children with AIS.

The Recognition of Stroke
In many textbook definitions of stroke, a sudden or rapidly developing onset of symptoms is said to be one of the cardinal features distinguishing stroke from other neurological disorders. In children, the clinical recognition of stroke is often difficult, leading to a considerable time delay between the onset of symptoms and the first encounter with a health care provider. The frequent insidious debut, with a progressive, stuttering, or recurrent course of symptoms as demonstrated in the current study, may very well be responsible for the late acknowledgement of stroke being the cause of the child’s neurological deficits. We have recently shown that in 42% of children with ischemic stroke, the initial symptoms were wrongly attributed to another neurological disorder than stroke.

Pediatricians and (pediatric) neurologists should be aware of the high likelihood of a nonabrupt onset of symptoms in children with AIS, which could certainly lead to a more rapid diagnosis of stroke. Although the safety of thrombolytic therapy in children has not been established and thrombolysis should therefore not yet be routinely applied in childhood AIS, both the nonacute onset of deficits, and the large delay until hospitalization severely hinder the potentially beneficial future application of thrombolysis in children with AIS.

Onset Predicts Etiology
In children with dissection and cardiac stroke, as well as in many patients with cryptogenic stroke, an embolic or thrombotic mechanism may be responsible for stroke. In 18 of these 26 children (69%), the onset of symptoms was abrupt. In contrast, 23 of the 30 (77%) children with the presumed inflammatory arteriopathies TCA or PVA had a nonabrupt onset. The relatively high frequency of an abrupt mode of onset in children with a nonarteritic stroke is not an unexpected finding. It has been shown in adult stroke patients that a rapid onset of symptoms is a clinical criterion that is significantly associated with a cardiac source of embolus. It is easy to conceive that a cardiac embolus, or a distal artery-to-artery embolization originating from proximal dissection or atherosclerosis, leads to acute occlusion of a major cerebral artery, giving rise to a sudden onset of neurological deficits. The abrupt onset in our 5 patients with anterior circulation arterial dissection is in agreement with a distal embolic occlusion. The tempo of onset was nonabrupt in all 3 children with posterior circulation dissection, of whom 2 had basilar artery thrombosis. The reason for this different mode of onset is unknown. It is, however, in accordance with the finding that 65 of 95 adults with proven basilar artery occlusion or bilateral distal vertebral artery occlusion had a nonacute onset of symptoms.

The nonabrupt symptoms in most children (77%) with inflammatory arteriopathies has not been previously reported, and has several possible explanations. Cerebral infarcts in TCA and PVA are located in the vascular territory of the lenticulostriate perforators that originate from the proximal part of the middle cerebral artery. The configuration of many of these infarcts is consistent with the involvement of multiple perforating arteries, rather than a small lacunar infarct in the territory of one single perforator. A stuttering, recurring, or progressive onset of symptoms in TCA and PVA could represent the stepwise or sequential occlusion of the origin of several perforators, caused by progression of middle cerebral artery arterial wall inflammation, or progressive thrombotic vascular obliteration. Interestingly, a similar mechanism has been proposed to play a role in the pathogenesis of progressive stroke in adults with lacunar infarction. Radiographical features (eg, frequent beading and multifocal stenoses) of the course of the arteriopathy (possible gradual initial progression in the first months, followed by stabilization, scarring, or resolution of abnormalities) and the temporal relation with preceding infections (Varicella-Zoster Virus) are suggestive of an inflammatory, vasculitic origin of TCA and PVA. In some patients, initial MRA immediately after stroke is normal, although infarction is already visible, and only follow-up vascular imaging reveals the arteriopathy. This may indicate that in the acute stage anterior cerebral artery or middle cerebral artery vessel wall inflammation causes obliteration of the origin of these perforators that are too small to be visualized with MRA, before visible stenosis of the parent artery occurs.

Practical Implications
The findings of this study may help in the prioritization of ancillary investigations in children with ischemic stroke diagnosed. Although the diagnostic work-up of AIS should include vascular imaging, cardiac evaluation, and prothrombotic testing, patients with a nonabrupt onset of symptoms have a significantly increased risk of underlying arteriopathy and should undergo vascular imaging as soon as possible, whereas in children with acute onset stroke, who are more likely to have embolic causes, the search for cardiac and arterial sources of embolus (dissection) seems to have first priority. In a later stage, thorough investigations for possible additional risk factors contributing to stroke, such as prothrombotic conditions, should be performed in every child with AIS.

A rapid determination of the exact cause of childhood stroke may have important consequences for the choice of acute treatment and secondary prevention. At present, there is no evidence, and often even no consensus, for treatment strategies in pediatric ischemic stroke. However, future randomized controlled trials designed to demonstrate the efficacy and safety of different therapies in various subtypes of childhood stroke would obviously require an early and accurate etiological stroke diagnosis. Since the first description of TCA in 1998, longitudinal vascular imaging has more and more demonstrated the high prevalence of inflammatory nonprogressive arteriopathies such as TCA and PVA in
children with stroke.1,2,3,4,19,20 In our cohort of 98 children with AIS, >30% of patients experienced an inflammatory arteriopathy. These patients carry a relatively high risk of recurrence during the first few months after stroke.2,3 and many children are left with neurological deficits.3 Therefore, a short course of corticosteroids (possibly in combination with antiviral medication) could potentially be beneficial in this subgroup.7 The present study shows that a nonabrupt onset of symptoms is associated with a highly increased risk of particularly inflammatory arteriopathies and has a significant discriminatory power. Therefore, early recognition of possible TCA and PVA by means of acute vascular imaging in children with a stuttering, recurring, or progressive stroke onset could in the future lead to rapid initiation of anti-inflammatory treatment, thus improving prognosis by preventing further deterioration and reducing the risk of stroke recurrence.

Sources of Funding
Dr DeVeber is supported by a Stroke investigator Award from the Heart and Stroke Foundation of Ontario.

Disclosures
None.

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Stroke. 2007;38:298-302; originally published online December 28, 2006;
doi: 10.1161/01.STR.0000254484.10680.c6
Stroke is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0039-2499. Online ISSN: 1524-4628

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