Special Article

Neurologic Outcome in Survivors of Childhood Arterial Ischemic Stroke and Sinovenous Thrombosis

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ABSTRACT

Ischemic stroke during infancy and childhood has the potential for life-long morbidity. Information on the neurologic outcome of children who survive ischemic stroke is lacking. Children surviving ischemic stroke between January 1, 1995 and July 1, 1999 were prospectively followed. Neurologic deficit severity was based on the Pediatric Stroke Outcome Measure (PSOM) developed in this study and parental response to two recovery questions. Predictor variables for poor outcome were tested. One-hundred twenty-three children with arterial ischemic stroke and 38 with sinovenous thrombosis were followed for a mean of 2.1 years (range, 0.8 to 6.6 years). The primary outcome based on PSOM assessment was: normal, 37%; mild deficit, 20%; moderate deficit, 26%; and severe deficit, 16%. The secondary outcome was full recovery in 45% of patients, based on parental response. The primary and secondary outcome measures were moderately correlated ($P < .001$; $K = 0.5$). In bivariate analysis, arterial stroke type, male gender, age of at least 28 days, presence of associated neurologic disorders, and need for rehabilitation therapy after stroke were predictors of poor outcome ($P < .05$). Multivariate analysis showed that only arterial ischemic stroke, associated neurologic disorders, and presence of rehabilitation therapy were independent predictors of poor outcome ($P < .02$). Poor outcome in children after ischemic stroke is therefore frequent and more likely in the presence of arterial stroke, rehabilitation therapy, and associated neurologic disorders, which justifies clinical trials of treatment strategies in childhood ischemic stroke. (*J Child Neurol* 2000;15:316–324).

Ischemic stroke during infancy and childhood is increasingly recognized, and has the potential for significant life-long morbidity. There are several reasons for the increasing frequency of diagnosis of ischemic stroke over the past decade. These include more sensitive radiographic tests; survival of children with previously life-threatening primary disorders who develop ischemic stroke as a consequence of the primary disease or its treatment; and an increasing index of suspicion by pediatricians. The long-term neurologic outcome of children who have had an ischemic stroke is important, for reasons that include the morbidity suffered by affected children and the economic cost to society. Information about outcome after stroke is critical for selection of potentially beneficial interventions for testing in clinical trials with the goal of improving neurologic outcome.

The neurologic morbidity following ischemic stroke in children is reported in a small number of publications; incidences of adverse neurologic outcomes range from 50% to 90%.[1–5] Neonates and basal ganglia infarcts may have a better prognosis.[6–9] The wide variation of reported adverse outcomes reflects both the design of the studies, which usually are retrospective, have small sample sizes, and lack a standardized outcome measure, and the relatively recent availability of computed tomography (CT) and magnetic resonance imaging (MRI). Studies completed prior to the widespread availability of CT and MRI likely missed a milder spectrum of ischemic stroke and mislabeled children with other conditions. There is an urgent need for data regarding the outcome of children with ischemic stroke and accurate age-related predictors of neurologic outcome.

Received Sept 13, 1999. Accepted for publication Sept 24, 1999.

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Presented in part at the Childhood Cerebrovascular Disease Conference in London, UK, September 9, 1998.

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A prospective, longitudinal outcome study using a standardized neurologic assessment of infants and children surviving both arterial ischemic stroke and sinovenous thrombosis was performed at two children's hospitals in Ontario between January 1, 1992 and July 1, 1999. The objectives were to define the immediate and, more importantly, long-term predictors of neurologic outcome in children surviving ischemic stroke.

METHODS

Patient Population

The study was conducted at The Hospital for Sick Children, Toronto, Ontario, Canada and the Children's Hospital at Chedoke-McMaster, Hamilton, Ontario, Canada between January 1, 1992 and July 1, 1999. Children between term neonate age (<36 weeks of gestational age) and 18 years of age were eligible for the study if they had had either arterial ischemic stroke or sinovenous thrombosis after January 1, 1992 and survived. Children were identified at both hospitals by referral to specialized stroke clinics, and by performing health records searches with appropriate International Classification of Disease (ICD) codes on an annual basis. The following ICD-9 codes were used: 433, occlusion and stenosis of precerebral arteries; 434, occlusion of cerebral artery; 435, transient cerebral ischemia; 436, acute but ill-defined cerebrovascular disease; 437.4, cerebral arteritis; 437.5, moyamoya; 437.6, thrombosis of intracranial venous sinus; 438, late effects of cerebrovascular disease; and 325, intracranial sinus venous thrombosis. Children meeting the inclusion criteria were identified, and a standardized review of their health records conducted. Those children surviving their initial stroke and referred to the stroke clinics were examined using a standardized Pediatric Stroke Outcome Measure (PSOM) between January 1, 1995 and July 1, 1999.

Diagnostic Criteria of Ischemic Stroke

The diagnosis of ischemic stroke met strict clinical and radiographic criteria. Both clinical and radiographic criteria were required for inclusion.

Clinical Criteria

For infants and children older than 1 month, the diagnostic criterion for arterial ischemic stroke was sudden onset of a focal neurologic deficit of transient or permanent duration. For neonates with arterial ischemic stroke and children of any age with sinovenous thrombosis, criteria were seizures, lethargy, or focal neurologic deficit. Neonates who had presumed prenatal or perinatal infarcts that were not diagnosed in the neonatal period but later in infancy were excluded.

Radiographic Criteria

Radiographic reports in the clinical record and radiographic films were reviewed for each patient by the study neurologists to confirm diagnosis and classify each event as either arterial ischemic stroke or sinovenous thrombosis. For classification as arterial ischemic stroke, definite evidence on CT or MRI of focal infarction in a vascular distribution was required. For classification as sinovenous thrombosis, definite thrombosis seen in the cerebral veins or sinuses on either MRI, magnetic resonance venography, or conventional angiography was required. Definite evidence of sinovenous thrombosis on CT or computed tomographic venogram was accepted only for infants older than 1 month of age and children.

Clinical Information

A standardized clinical questionnaire was developed as part of the PSOM and completed for all children. The questionnaire was supplemented by health-record review. The following clinical information was obtained:

Initial Stroke

Stroke type, gender, age, and presenting clinical features such as seizures, hemiparesis, decreased level of consciousness, and headaches were noted. Associated neurologic disorders occurring at the time of the stroke with the potential to cause neurologic insult were recorded, including the presence of meningitis, hypoxic-ischemic injury, status epilepticus (seizures lasting more than 45 minutes), and head trauma with loss of consciousness. Based on the age and stroke type, four subgroups were defined for descriptive purposes: neonatal arterial ischemic stroke, neonatal sinovenous thrombosis, older arterial ischemic stroke, and older sinovenous thrombosis.

Past History

Associated neurologic disorders found prior to stroke were recorded, including developmental or language delay, learning disability, attention-deficit disorder, seizure disorder, and remote major head injury.

Medications

Antithrombotic agents taken at presentation with stroke, and subsequently, were recorded. These included heparins (unfractionated and low molecular weight), warfarin, and aspirin.

Outcome

Information on outcome during the follow-up period included a detailed history of any persistent neurologic deficits, seizures, or migraine headaches, as well as occurrence of transient ischemic attacks, recurrent ischemic stroke, and death. The presence, type, and frequency of current and past rehabilitation were also recorded.

Radiographic Information

For arterial ischemic stroke, infarcts were classified as a large vessel territory (full anterior, middle, or posterior cerebral artery territory) or small vessel territory (lenticulostriate artery territory). Arterial ischemic stroke was further classified by hemisphere (right, left, both), number (single or multiple concurrent), character (bland or hemorrhagic), recurrence of infarct or transient ischemic attack (present or absent), and presence or absence of basal ganglia infarction. For sinovenous thrombosis the presence of a venous infarct was noted.

Outcome Measure for Ischemic Stroke

Development

The investigators developed a standardized Pediatric Stroke Outcome Measure. The PSOM neurologic examination was adapted, with permission, from pediatric neurologic examination scales developed

for use in other childhood populations.[10,11] The final PSOM was a composite of clinical and radiographic information as outlined above and a detailed neurologic examination. The measure was systematically used in the stroke clinic from January 1, 1995.

Neurologic Examination

The neurologic examination of the PSOM contained 115 test items ordered developmentally in the areas of behavior, mental status, cranial nerves, motor functions (developmental, fine and gross motor, and motor tone, power, reflexes, and involuntary movements), sensory function, cerebellar function, and gait function. At the completion of the examination, a deficit severity score ranging from 0 (no deficit) to 2 (severe deficit) was assigned for each of five spheres: right sensorimotor (including motor, visual, hearing, and somatosensory function), left sensorimotor, language production, language comprehension, and cognitive and behavioral performance. The patient was assigned an overall Deficit Severity Score of normal, mild, moderate, or severe for each assessment, based on the combination of scores in the individual spheres of the PSOM (Table 1). Neurologic assessments were performed in outpatient stroke clinics by the three study neurologists (Drs deVeber, Curtis, and MacGregor) at standardized intervals calculated from the child's stroke. Infants 12 months of age or less at the time of stroke were evaluated at 3 to 6 months, 9 months, 12 months, 18 months, and 24 months of age, then annually. Children older than 12 months at the time of stroke were evaluated 3 to 6 months and 12 months after the ischemic stroke and then annually.

Primary Outcome

The primary outcome was based on the most recent PSOM assessment. Neurologic deficits were described by their severity and type. For statistical analyses, the PSOM Deficit Severity Score was classified into two categories: good outcome (normal and mild deficit) and poor outcome (moderate and severe deficit) (Table 1).

Secondary Outcome

The secondary outcome was complete recovery versus incomplete recovery, based on parental response to two questions modified from the Euroqual measure.[12–14] These were (1) Has your child recovered completely from his or her stroke? and, (2) Does your child need extra help in day-to-day activities compared with other children his or her age? Outcome was categorized as complete recovery if the parent responded yes to question 1 and no to question 2, indicating no extra help was needed. Otherwise, outcome was categorized as incomplete recovery. The modified Euroqual questions were applied systematically by one neurologist on a subset of patients in face-to-face interviews during clinical assessments from May 1996 to July 1999.

Table 1. Deficit Severity and Primary Outcome Scoring for Pediatric Stroke Outcome Measure (PSOM)

Outcome Classification	*Definition**
Good	
Normal	Score = 0 in all five spheres†
Mild deficit	Score = 0.5 in one sphere only
	Score = 0.5 in one sphere only
Poor	
Moderate deficit	Score = 0.5 in two, three, or four spheres
	Score = 1 in one sphere and 0.5 in one sphere
	Score = 1 in one sphere only
Severe deficit	Score = 0.5 in all five spheres
	Score = 1 in one sphere plus 0.5 in two spheres
	Score = 1 in at least two spheres
	Score = 2 in at least one sphere

*0 = No impairment, normal function; 0.5 = minimal to mild impairment, normal function; 1 = moderate impairment, decreased function; 2 = severe impairment, loss of function.
†Right sensorimotor, left sensorimotor, language expressive, language comprehensive, and cognitive and behavior.

Predictors of Outcome

All Patients

Predetermined categorical predictor variables comprised stroke type (arterial ischemic stroke or sinovenous thrombosis), sex, associated neurologic disorder, seizures, hemiparesis or decreased level of consciousness at presentation, antithrombotic therapy, and rehabilitation therapy. Age was handled both as a continuous variable (in decimal years) and as a categorical variable (either less than 1 month, or 1 month to 18 years). Delay to diagnosis was handled as a continuous variable from 0.001 to 100 days.

Patients With Arterial Ischemic Stroke

Additional predictor variables defined for children with arterial ischemic stroke were: the number of infarcts (single or multiple concurrent); hemisphere (right, left, or both); large versus small vessel territory; presence of hemorrhage into an infarct; basal ganglia infarcts; and recurrent arterial ischemic stroke.

Patients With Sinovenous Thrombosis

For sinovenous thrombosis, the presence of venous infarct was analyzed.

Statistical Analysis

Statistical analysis was performed using StatView version 5.0.1 (SAS Institute, USA, second edition, March 1998).

The component categories for the primary outcome—normal, mild deficit, moderate deficit, and severe deficit—were described for all patients, as well as the four subgroups: neonatal arterial ischemic stroke (< 28 days old at event), neonatal sinovenous thrombosis, older arterial ischemic stroke (> 28 days old at event), and older sinovenous thrombosis. Next, the primary outcome (good versus poor) was described in all patients by frequency distributions for all the predictor variables. A bivariate analysis was performed, testing each predictor variable listed above against the primary outcome. Chi-squared values and associated probabilities were calculated. A one-way analysis of variance (ANOVA) was performed to test the continuous predictor variables age at event, delay in diagnosis, and interval from event to testing against the primary outcome. Predictor variables found to be significant ($P < .05$) were entered into multiple logistic regression models for each outcome, with significance set at $P < .02$. Results were presented as odds ratios with their 95% confidence intervals.

The secondary outcome, obtained from responses to the two modified Euroqual questions, was tested as described for the primary outcome.

RESULTS

Patient Population

As of January 1, 1995 there were 59 children with ischemic stroke diagnosed after January 1, 1992 who were being followed by the two stroke study clinics. A further 104 children with ischemic stroke were referred between January 1, 1995 and May 1, 1999, for a total of 163 children forming the basis of the following analyses (cohort). Based on chart reviews, there were 115 living children who did not attend the stroke clinics (noncohort). Comparison with the study cohort is provided. In the cohort, 125 (77%) of 163 had arterial ischemic stroke, 38 (23%) had sinovenous thrombosis, and 2 (1%) had both arterial ischemic stroke and sinovenous thrombosis. In the noncohort, 90 (78%) of 115 had arterial ischemic stroke and 25 (22%) had sinovenous thrombosis. There were no differences in stroke type (P = .49), sex (P = .72), mean age (P = .34), proportion of neonates (P = .71), and presence of antithrombotic treatment (P = .94) between the two groups.

Clinical Features

Arterial ischemic stroke occurred 3.2 times more frequently than sinovenous thrombosis. The clinical features of the patients are presented for the two major stroke types, arterial ischemic stroke and sinovenous thrombosis, in Table 2. Nearly one third (32%) of the cohort were neonates, and 56% were boys. Mean age at stroke was 5.05 years (SD, 5.17; range, 0 to 17.8). There were 33 neonates with arterial ischemic stroke, 18 neonates with sinovenous thrombosis, 90 older infants and children with arterial ischemic stroke, and 19 older infants and children with sinovenous thrombosis. Two older children had both arterial ischemic stroke and sinovenous thrombosis. At presentation, 52% of patients had seizures and 73% had hemiparesis. Associated neurologic disorders were present in 25%. Treatments included antithrombotic therapy for 55% of patients (27% of cases of neonatal arterial ischemic stroke, 25% of neonatal sinovenous thrombosis, 81% of older arterial ischemic stroke, and 67% of older sinovenous thrombosis), and rehabilitation therapy for 52%. Patients in the group receiving antithrombotic therapy most often were older arterial ischemic stroke patients, of whom 89% received aspirin therapy. During follow-up, 34% had headache, 15% had seizures, and 4% had transient ischemic attacks. Recurrent cerebral thromboembolic events, including transient ischemic attacks, occurred in 16 cases of arterial ischemic stroke and 5 cases of sinovenous thrombosis. No child died during follow-up.

Table 2. Clinical Features of Children With Ischemic Stroke

Characteristic	*Patients With AIS, n (%)**	*No. With SVT, n (%)**
Initial stroke		
Male	78 (63)	14 (37)
Female	45 (37)	24 (63)
Mean age ± SD (years)	4.7 ± 5.1	3.8 ± 5.2
Age range	0–17.8	0–17.1
Neonate	33 (27)	19 (50)
Nonneonate	90 (73)	19 (50)
Seizures	44 (49)	14 (64)
Hemiparesis	68 (76)	13 (57)
Associated neurologic disorders	26 (21)	14 (39)
Antithrombotic treatment		
No treatment	42 (42)	15 (60)
Treatment	57 (58)	10 (40)
Heparin	12 (12)	6 (24)
Warfarin	6 (6)	5 (20
Acetylsalicylic acid	52 (53)	7 (28)
Rehabilitation therapy	56 (58)	7 (28)
Follow-up		
Seizures	12 (13)	6 (23)
Headaches	32 (33)	9 (35)
Transient ischemic attacks	3 (3)	1 (4)
Recurrence	11 (11)	2 (15)

*Proportion of patients with AIS and SVT (data not available on all patients).
AIS = arterial ischemic stroke; SVT = sinovenous thrombosis.

Radiographic Features

In arterial ischemic stroke patients, infarcts were usually bland (86%) and single (78%). Infarcts involved large artery territory nearly as commonly as small artery territory (40% versus 45%, respectively, and 15% in both territories). Patients with arterial ischemic stroke were nearly as likely to have infarcts in the right (40%) as compared to the left (49%) hemisphere; in 11% of patients, both hemispheres were involved. Basal ganglia infarction was present in 39% of arterial ischemic stroke patients. Venous infarcts were present in 39% of sinovenous thrombosis patients.

Outcome Measures

Neurologic Examinations

A total of 332 PSOM neurologic assessments were performed in the cohort of 163 patients during the study interval. Seventy-three patients had a single follow-up assessment, 40 had two assessments, and 50 had three or more assessments. In the 90 patients having two or more assessments over time, 38 (42%) patients had no change in PSOM outcome category, 23 (26%) appeared to improve, and 29 (32%) appeared to worsen. Children with worsening neurologic deficits included 10 neonates with normal initial examinations who demonstrated abnormalities with maturation during the 18 months following their event.

Primary Outcome

The last PSOM examination on which primary outcome was based was performed at a mean of 2.07 years (SD, 1.49; range, 0.01 to 17.59) following initial stroke. PSOM results for all patients were: normal, 39%; mild deficit, 20%; moderate deficit, 25%; and severe deficit, 16%. This resulted in a primary outcome classification of good in 59% (53.6% of cases of arterial ischemic stroke and 82% of sinovenous thrombosis) and poor in the remainder. Primary outcome was described for the four major patient groups: neonatal arterial ischemic stroke (33 patients), neonatal sinovenous thrombosis (19 patients), older arterial ischemic stroke (90 patients), and older sinovenous thrombosis (19 patients) (Table 3). Patients

with arterial ischemic stroke and older infants and children had the worst outcome. The best outcome was in neonates with sinovenous thrombosis in whom 16 of 19 had normal or mild deficit (Table 3). Nearly all deficit types were represented in all stroke types, but unilateral sensorimotor deficit was present in only 18% of sinovenous thrombosis patients versus 57% of arterial ischemic stroke patients (Table 4). Speech deficits and cognitive or behavioral deficits were rare, present in only 15% of patients with arterial ischemic stroke and 11% with sinovenous thrombosis.

Secondary Outcome

The two modified Euroqual questions were administered at final assessment in a subset of 102 patients evaluated by one neurologist. Forty-five percent of parents classified their children as fully recovered and 55% as not fully recovered. Secondary outcome results are provided for subgroups of neonatal arterial ischemic stroke, neonatal sinovenous thrombosis, older arterial ischemic stroke, and older sinovenous thrombosis (Table 5). For cases of sinovenous thrombosis and neonatal arterial ischemic stroke, parents were twice as likely to describe their child as fully recovered than as nonrecovered, but for older children with arterial ischemic stroke, the opposite was true (18 recovered versus 38 not).

Comparison of PSOM and Euroqual

PSOM and Euroqual outcomes at the last clinic visit are summarized in Tables 3 and 5. The two measures were moderately correlated ($P < .001$; K = 0.5). When the response to the recovery question was in disagreement with the PSOM classification on the same day, parents were equally as likely to have overestimated or underestimated recovery compared to the PSOM in all but one group. In neonates with arterial ischemic stroke, 20% of parents classified their child as fully recovered when the PSOM score was abnormal, but none classified their child as not fully recovered when PSOM was normal.

Predictors of Outcome

Primary Outcome

The primary study outcome was "poor outcome" by PSOM classification. A bivariate analysis between potential predictors and primary outcome was performed in all patients (Table 6). Arterial stroke type, male sex, older age in infants and children, associated neurologic disorders, and need for rehabilitation therapy after stroke predicted a poor outcome ($P < .05$). Subsequent logistic regression modeling showed that only arterial ischemic stroke, associated neurologic disorders, and presence of need for rehabilitation therapy were independent predictors of poor outcome ($P < .02$) (Table 7).

For patients with arterial ischemic stroke, bivariate analysis showed that presence of associated neurologic deficit ($P = .007$), antithrombotic therapy ($P = .04$), rehabilitation therapy ($P = < .0001$), and infarcts in both hemispheres ($P = .04$) were predictors of poor outcome. Nonpredictive features were: basal ganglia infarcts ($P = .43$), hemorrhagic versus bland infarcts ($P = .56$), multiple versus single infarcts ($P = .24$), and large versus small artery territory infarcts ($P = .35$). In patients with sinovenous thrombosis, the presence of venous infarcts did not predict poor outcome ($P = 1.00$).

Secondary Outcome

Bivariate analysis between pre-assigned predictor variables and the modified Euroqual questions showed that nonneonate ($P = .0218$), seizures ($P < .0001$), hemiparesis at presentation ($P < .0001$), associated neurologic disorders ($P = .040$), antithrombotic therapy ($P < .0001$), rehabilitation therapy ($P < .0001$), and stroke recurrence ($P = .043$) were all related to incomplete recovery. Stroke type was not predictive. Multivariate analysis, however, showed that

Table 3. Primary Outcome by Pediatric Stroke Outcome Measure (PSOM)

	Neonatal		*Older*		*All (%)*
	AIS	*SVT*	*AIS*	*SVT*	
PSOM Classification	*(n = 33)*	*(n = 19)*	*(n = 90)*	*(n = 19)*	*(N = 161)*
Normal	*11*	*14*	*28*	*10*	*63 (39)*
Mild	*9*	*2*	*16*	*5*	*32 (20)*
Total with good outcome	20	16	44	15	95 (59)
Moderate	*11*	*2*	*25*	*3*	*41 (26)*
Severe	*2*	*1*	*21*	*1*	*25 (16)*
Total with poor outcome	13	3	46	4	66 (41)

Subtotals in italics.
*Excludes two patients with both AIS and SVT.
AIS = arterial ischemic stroke; SVT = sinovenous thrombosis.

Table 4. Neurologic Deficit Type From Pediatric Stroke Outcome Measure (PSOM)

	Neonatal		*Older*		*All (%)*
	AIS	*SVT*	*AIS*	*SVT*	
PSOM Deficit Type	*(n = 33)*	*(n = 19)*	*(n = 90)*	*(n = 19)*	*(N = 161)*
No deficit	11	14	28	10	63 (39)
Bilateral sensorimotor	2	3	9	3	17 (11)
Right only sensorimotor	13	1	24	2	40 (25)
Left only sensorimotor	6	1	27	3	37 (23)
Expressive speech	4	1	16	3	24 (15)
Receptive speech	1	0	10	1	12 (7)
Cognitive or behavioral	1	0	15	1	17 (11)

Table excludes two patients with both AIS and SVT; patients represented more than once if they had multiple deficits; mild, moderate, or severe grade deficits counted as deficit present.
AIS = arterial ischemic stroke; SVT = sinovenous thrombosis.

Table 5. Secondary Outcome: Parental Response to Modified Euroqual Questions

	Neonatal		*Older*		*All (%)**
	AIS	*SVT*	*AIS*	*SVT*	
Parental Impression of Complete Recovery	*(n = 22)*	*(n = 10)*	*(n = 56)*	*(n = 11)*	*(N = 99)*
Yes	14	7	18	7	46 (45)
No	8	3	38	4	53 (55)

*Excludes two patients with both AIS and SVT.
AIS = arterial ischemic stroke; SVT = sinovenous thrombosis.

Table 6. Predictors of Outcome in Childhood Stroke: Bivariate Analysis of All Patients

Predictor	*Number With Good Outcome (%) (n = 95)*	*Number With Poor Outcome (%) (n = 68)*	*P Value*
Stroke type			
Arterial ischemic stroke	64 (52)	59 (48)	.034
Sinovenous thrombosis	31 (82)	7 (18)	
Both	2 (2)	0	
Gender			
Male	47 (51)	45 (49)	.052
Female	48 (68)	23 (32)	
Age			
Neonate (28 days or younger)	46 (69)	16 (31)	.054
Nonneonate (more than 28 days)	59 (53)	52 (47)	
Seizures at stroke			
Present	34 (27)	25 (74)	.41
Absent	35 (46)	19 (54)	
No data	26	24	
Hemiparesis at stroke			
Present	49 (60)	33 (40)	.27
Absent	21 (68)	10 (32)	
No data	25	25	
Associated neurologic disorder			
Present	16 (40)	24 (60)	.03
Absent	73 (63)	43 (37)	
No data	2	1	
Antithrombotic therapy			
Present	41 (59)	28 (41)	.18
Absent	37 (65)	20 (35)	
No data	17	20	
Rehabilitation therapy			
Present	26 (41)	38 (59)	< .001
Absent	50 (85)	9 (15)	
No data	19	21	

rehabilitation ($P < .0001$) was the only factor that independently predicted a poor outcome.

DISCUSSION

Ischemic stroke during childhood can be a devastating disorder, with long-term morbidity and, in some cases, mortality. In order for new stroke therapies that are currently available for adults to benefit children, identification of high-risk groups of children is necessary. Accurate data on outcome and predictors of outcome in children with stroke are lacking. In this prospective study, the neurologic outcome following stroke was assessed in 163 children over several years with multiple standardized assessments. We found that over 41% of patients had moderate or severe deficits on neurologic examination and 45% had incomplete recovery according to parents. Arterial stroke type and presence of associated neurologic deficits or rehabilitation therapy were found to predict worse outcome. Also, two outcome measures for this population, the PSOM and modified Euroqual questions, were developed and initial tests performed.

This study was a longitudinal outcome study. From the time of their stroke after January 1992, all patients were followed in specialized stroke clinics; standardized outcome assessments began with the initiation of the PSOM in January 1995. Not all children meeting the criteria were included in the study; however, those not attending the clinic did not appear to differ in important ways from the study cohort, and it is felt that the results can be generalized to children with stroke in most clinical settings.

Children with both arterial ischemic stroke and sinovenous thrombosis were included in the study. Ischemic stroke can be defined as focal cerebral infarction secondary to occlusion of either the arterial (arterial ischemic stroke) or venous (sinovenous thrombosis) circulation within the central nervous system. Sinovenous thrombosis can be included in the definition, although parenchymal infarcts are not uniformly present in this condition. In both arterial and

Table 7. Predictors of Outcome: Logistic Regression Analysis of All Patients

Predictor Tested	*Reference Category*	*Moderate or Severe Neurologic Deficit*
Stroke type		Odds Ratios
Sinovenous thrombosis	Arterial ischemic stroke	0.21 (0.06–0.64)*
Age		
Nonneonate	Neonate	0.9 (0.39–2.09)
Sex		
Female	Male	0.55 (0.26–1.20)
Associated neurologic disorder		
Yes	No	3.23 (1.3–8.02)*
Rehabilitation		
Yes	No	5.24 (2.06–13.27)†
Constant		0.27 (0.11–0.64)

*$P < .01$.
†$P < .001$.

venous occlusion, the mechanism usually involves cerebral thrombosis or embolism. Therefore, disorders predisposing to thrombosis and treatment with antithrombotic agents are important issues in both of these conditions. Both pediatric arterial ischemic stroke and sinovenous thrombosis have been reported in numerous case reports and case series.[2,15–19] Strict clinical and radiographic diagnostic criteria were maintained; for example, definitive evidence of diagnostic features on neuroimaging was required. For sinovenous thrombosis in particular, only confirmed MRI or angiography were accepted in neonates because CT can yield false positive results.[20,21]

We included neonates diagnosed at the time of acute event in the study. It is important to study the continuum of ischemic stroke at various ages in a given population, in order to appreciate the similarities and differences between neonates and older infants and children. Neonates have occasionally been included in childhood stroke studies,[2,22] but usually are reported separately.[6,23] We excluded older infants diagnosed months after a presumed neonatal or prenatal stroke, since such infants are diagnosed with ischemic stroke only because of the presence of a significant neurologic deficit, usually hemiparesis. Inclusion of these infants would result in an overestimate of deficits from neonatal stroke. Children with associated neurologic disorders prior to or concurrent with the stroke were also included in the study. We did this in order to make the results applicable to other populations of children, since associated neurologic disorders frequently accompany stroke.

Outcome measures for childhood stroke are lacking. A useful assessment measure must accurately define a clinically and functionally relevant outcome. Ideally, both a standardized questionnaire for obtaining clinical features potentially predictive of stroke outcome and a classification of the types of stroke should be available. In this study, the PSOM was developed and tested in 332 examinations of 163 children with stroke. The PSOM was found to accurately classify children with either good or poor neurologic outcome, as well as define clinical and radiographic predictors of stroke outcome.

Objective standardized outcome measures for children with acute unilateral focal cerebral lesions did not exist at the start of this study. In 1992, available published childhood neurologic assessments[24–26] were reviewed and rejected, because they were designed for diffuse, bilateral, or progressive central nervous system disorders (such as cerebral palsy, adrenoleukodystrophy, and human immunodeficiency virus encephalopathy). Two available scales, unpublished at the time, were somewhat suited to the purpose of this study; features of these scales were incorporated into the PSOM with the authors' permission. The stroke reporting measure used in the Stroke Trial in Sickle Cell Disease study[11] was specifically designed for children with stroke (and is the only such scale in existence), but does not encompass the infant and toddler age groups, nor allow multiple levels of severity to be graded. Dr I. Rapin had developed a triad of age-related outcome measures (infancy, preschool, and school-age) that were sufficiently detailed for the purpose of this study, Likert scaled, and able to be adapted to assess independent unilateral sensorimotor functions.[10] Examination items were combined in the PSOM into one form for all ages, ordered in a maturational continuum from birth to the teenage years. The Likert-type scoring was modified to emphasize the functional impact of deficits and to score sensorimotor items separately for right and left. A standardized stroke-oriented clinical questionnaire and a section for simple radiographic classification of stroke features was added.

In defining the good and poor primary outcomes based on the PSOM for this study, mild deficits were included in the good outcome category, since merely detecting an abnormality on examination (for example, a spastic catch in an arm) that does not have clear functional consequences is of questionable significance. This classification may have resulted in an underestimate of abnormal outcomes, but it was preferred to underestimate rather than overestimate mild abnormalities. The most significant limitations of the PSOM are likely in the cognitive and language assessment areas, in which standard psychometric testing would undoubtedly be more sensitive and reliable than the neurologic examination items. We have not performed full interobserver reliability testing for the PSOM measure, but interobserver reliability pilot data were obtained during the course of this study. Two neurologists performed same-day assessments on 10 children with a range of ages from newborn to 13 years, a range of deficit severity from normal to severe, and a range of stroke types from large artery territory to small artery territory and sinus thrombosis. A concordance rate of 91% for item scoring was found.

It is important to define outcome after stroke in terms of functional dependence or independence, as well as to incorporate quality of life when feasible. This has increasingly been the focus of outcome stroke scales used in adults. Usually, the outcome measures used in adults with stroke[27,28] cannot be used for infants and young children, since the necessary cooperation and skills required for such assessments are not present early in the developing child. However, the Euroqual simple questions approach could be applied to the population by using parent report. The Euroqual has been studied extensively as an outcome measure in adult stroke.[12–14] It is simple, easy to administer, has good validity and predictive value, and assesses quality of life in addition to presence of impairment. The two questions in the Euroqual measure that are most predictive of outcome are the recovery question and the independence question. These have been shown to be valid when completed by caregivers of stroke patients.[12] These two questions were adapted for parental response and for pediatric patients. Since most young children are normally dependent for day-to-day activities, it was necessary to add the phrase "compared with other children his/her age" when asking about independence and dependence. Good correlations with the PSOM major outcome categories ($P < .001$) were found, with an acceptable kappa value (0.5).

In this study population, arterial ischemic stroke occurred 3.2 times more frequently than sinovenous thrombosis, consistent with population-based studies in these conditions.[29] Nearly one third (32%) of the cohort were neonates, also consistent with observations that neonates are at particular risk for cerebral thromboembolism.[22,29] Poor outcome was found in 46% of infants and children with arterial ischemic stroke and 18% with sinovenous thrombosis. This study included only stroke survivors. The number of poor outcomes would be increased if deaths were included. The neurologic deficit rate reported here is consistent with some reports[3,5] but better than that reported in others,[1,2,4,15,30] in which more than 70% of children with stroke had residual motor deficits whether or not neonates were included. However, some of these studies have not clearly distinguished outcomes in hemorrhagic stroke from outcome in ischemic stroke. Outcome was found to be worse after arterial ischemic stroke than sinovenous thrombosis in the present study. This is perhaps to be expected, since the mechanism of cerebral damage differs between the two conditions. Indeed, in sinovenous thrombosis, nearly 50% do not have infarcts and may have no permanent damage. Also, sinovenous thrombosis has been shown previously to result in fewer motor deficits.[23,31,32] This is, to the authors' knowledge, the first study of outcome in children with arterial ischemic stroke and sinovenous thrombosis in one population.

Neonates had fewer poor outcomes (31%) than older infants and children; this may reflect a relative resistance of the neonatal brain to injury. However, the vulnerability of the neonatal brain to injury has been recently emphasized.[33] Enhanced plasticity of the developing central nervous system in infancy relative to childhood may enable more complete recovery in neonates, although evidence supporting this hypothesis is lacking. The authors believe that, due to the delay in appearance of neurologic deficit after neonatal stroke, even follow-up of several years may fail to detect the more subtle sequelae that are not evident in the as-yet immature brain. This has been discussed previously,[2,23] and is consistent with the finding of an increasing deficit over time in nearly one third of neonates with arterial stroke in this study. Other studies[6,7] have reported a high frequency of motor deficits (73% and 88%), cortical sensory deficits (34%), and seizure disorders (50%) after perinatal cerebral infarcts or hemorrhage. This may reflect the inclusion of infants with delayed diagnosis and delayed onset of hemiparesis, due to presumed prenatal or perinatal arterial infarcts.

Associated neurologic disorders were present in 25% of the patients in the current study. The presence of these disorders predicted a worse outcome. The deficits found in our study result from the effects of the stroke itself, as well as the effects of disorders predisposing to stroke, that can themselves contribute to neurologic deficit, such as meningitis. This is true of all unselected populations of children with stroke. No predictive effect of antithrombotic therapy, given to 55% of patients, was found. Usually, antithrombotic therapy, especially aspirin, the most prevalent in this study, is given for secondary prevention of stroke. Recurrent events, including transient ischemic attacks, occurred in only 10% of patients. This study was not designed to establish benefit or harm from antithrombotic treatments. Requiring rehabilitation therapy was strongly predictive of worse outcome, as would be expected.

Seizures at stroke onset have been reported to predict both worse intellectual outcome[34] and better outcome.[35] In our study, no predictive effect on outcome of seizures at onset was found. No influence on outcome of basal ganglia infarct location was found in arterial stroke patients. Basal ganglia infarction has been reported to predict better prognosis for motor handicap than cortical infarction,[8,9,36] although others have found worse outcome in this group.[30] Dystonia can develop after a latency as long as 9 years after cerebral infarct.[37] This further emphasizes the need for long-term prospective follow-up of infants and children with cerebral insults, in whom the nervous system is still developing. Other infarct features, including infarct volume (small versus large vessel territory) and presence of hemorrhagic components were not predictive in this study, and have not been evaluated by others in children with later-onset infarcts.

In summary, the first large-scale prospective outcome study following infants and children surviving both forms of childhood ischemic stroke, arterial ischemic stroke and sinovenous thrombosis, was performed. Two useful outcome measures were developed for this population, the PSOM and the modified Euroqual recovery questions. Arterial stroke type, presence of associated neurologic disorders, and the need for rehabilitation therapy were found to be strong and independent predictors of poor outcome. Other predictors need further study, since this study may not have had sufficient power to find predictive significance. The current study is continuing in order to further establish the reliability and validity of the outcome measures, define additional predictors of outcome in childhood ischemic stroke, and enable the development of clinical trials targeted to subgroups of patients with the worst outcomes.

Acknowledgments

The authors thank Dr Maureen Andrew for her invaluable ongoing research advice, Derek Stephens, MSc for statistical expertise, Dr Athen MacDonald for assistance in testing the PSOM, and Trish Domi, MA, Shelley Brazier, BA, and Collen Patterson, MSc for their excellent technical assistance in preparing this manuscript. This work was supported by the Bloorview Children's Hospital Foundation. Dr deVeber is supported by a Stroke Investigator Award from the Heart and Stroke Foundation of Ontario.

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