Original Article

Factors Predictive of Outcome in Childhood Stroke in an Asian Population

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Abstract

Introduction: While paediatric strokes are fairly uncommon, they are often associated with significant long-term disability. Diagnosis is often delayed because of the need to exclude conditions that mimic stroke. Understanding the outcomes related to stroke in children is important in the development of secondary prevention strategies. The aim of this study was to evaluate the epidemiology of childhood stroke in a tertiary paediatric unit in Singapore and to assess factors influencing outcome in these children. Materials and Methods: A retrospective case-note review of all childhood strokes presenting to the Children's Medical Institute (CMI) at the National University Hospital (NUH), Singapore between October 1999 and May 2006. Data collected include demographic factors, clinical presentation, diagnosis, subsequent management and follow-up using specific outcome measures. Results: Twenty-six children with a median age of 8.0 years at presentation were identified, comprising 15 ischaemic strokes (57.7%), 10 haemorrhagic strokes (38.5%) and 1 patient with both ischaemic and haemorrhagic lesions. The most common symptoms at presentation were seizures (15/26, 57.7%), lethargy (11/26, 42.3%), hemiparesis (10/26, 38.5%) and altered levels of consciousness (10/26, 38.5%). Vascular abnormalities accounted for 50% of strokes in our study population. The average length of follow-up was 33.2 months (range, 1 to 120) with only 11 children (11/26, 42.3%) achieving full recovery. Significant prognostic factors include altered consciousness and seizures at presentation, lesions in both cortical and subcortical locations, systemic disease aetiology, neurological deficits at discharge and seizures at the time of discharge. Conclusion: Long-term neurological, neuropsychological and functional impairment are common in survivors of paediatric strokes. Certain clinical features and lesion characteristics are useful indicators of prognosis in these children.

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Key words: Children, Haemorrhage, Infarct, Prognosis

Introduction

Strokes in childhood are generally considered to be rare with an incidence of about 2.7 per 100 000 children per year.[1] The aetiologies of stroke in children differ considerably from adults and multiple risk factors commonly co-exist. A large stroke registry in North America reported that a large proportion of children with arterial ischemic strokes had a recognised risk factor at presentation.[2] Congenital cardiac disease, vasculopathies such as Moyamoya disease, collagen vascular diseases and inherited abnormalities of coagulation are commonly implicated in paediatric strokes. Evaluation of disease aetiology is essential in the management of these patients as it impacts upon stroke recurrence and long-term quality of life.

Survival after stroke is generally better in children than adults.[3] However, studies have shown that these children face significant long-term neurological, cognitive and behavioural disturbances.[4,5] Schoenberg et al [6] found that up to 75% of survivors had residual neurological deficits 5 years after stroke. There have only been a handful of studies focusing on the outcome of strokes in childhood with several proposed prognostic factors including age at onset of stroke, symptoms at presentation, anatomical location of the lesion(s) and the underlying medical disorder.[7-10]

There is some evidence from adult studies that Asians are at higher risk of primary intracerebral haemorrhage and ischaemic stroke.[11] However, there is a paucity of data of childhood stroke in Asian patients. The aim of this study was to evaluate the epidemiology of childhood stroke in a tertiary paediatric unit in Singapore and to assess factors influencing outcome in these children.

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Materials and Methods

This was a retrospective case-note review of all childhood strokes presenting to the Children's Medical Institute (CMI) at the National University Hospital (NUH), Singapore between October 1999 and May 2006. Cases were identified by a search of the medical records database using the International Classification of Disease (ICD) codes version 9. Inclusion criteria comprised the presence of a focal neurological deficit lasting more than 24 hours, occurring between the age of 29 days and 18 years of life, as diagnosed by a paediatric neurologist and with radiological confirmation of ischaemic or haemorrhagic stroke. Children presenting with perinatal strokes, transient ischaemic attacks, traumatic brain injuries and neurological deficits resulting directly from an infective agent were excluded.

Data Evaluation

The medical records of eligible patients were reviewed for information concerning patient demographics, age at presentation, family history, underlying disease or risk factors, clinical state at presentation, investigations, diagnosis, treatment and follow-up.

Besides baseline investigations, stroke work up for the patients included screening for prothrombotic disorders (protein C, protein S, antithrombin III, prothrombin time, activated plasma thromboplastin time, autoimmune antibodies, homocysteine levels and genetic mutations of protein C, factor V Leiden, MTHFR and prothrombin mutations). Factor VIII and IX deficiency was also screened in patients with haemorrhagic strokes. Patients with raised lactate levels were further screened for common mitochondrial mutations associated with stroke.

Based on CT, MRI and/or MRA findings, ischaemic infarctions were sub-classified according to their vascular territories and the brain region affected – cortical or subcortical (internal capsule, basal ganglia, thalamus, brainstem, cerebellum). Haemorrhagic lesions were subdivided into subarachnoid, intraparenchymal and intraventricular haemorrhages.

Information on inpatient treatment included length of hospital stay, medical therapy and decompressive surgery.

Outcome Measures

Short-term outcome was measured in terms of clinical state at discharge as compared to that at presentation, length of outpatient follow-up and outpatient management including medication, physical, speech and occupational therapy. Long-term residual neurocognitive impairment was determined by neurological examination and neuropsychological evaluation, as proposed by Steinlin et al.[12]

In younger children under the age of 1 year at presentation, delay in developmental milestones was used as a means of assessing neurological outcome. The modified Rankin scale for assessing disability following stroke[13-15] was used for children presenting above 5 years of age.

Other outcome measures included the presence of motor and cognitive sequelae, speech difficulties, epilepsy and behavioural disturbances such as attention deficit hyperactivity disorder and aggressive tendencies.

Statistical Analysis

Data were analysed using the Statistical Package for the Social Sciences (SPSS) version 12.0 (Chicago, IL). Relationships between nominal variables were tested using Fisher's exact test and the Mann-Whitney U test was used for ordinal variables. The level of significance was set at 0.05.

Results

Demographics

A total of 26 children were identified in this study. There were 15 ischaemic strokes (15/26, 57.7%), 10 haemorrhagic strokes (10/26, 38.5%)and 1 child with Moyamoya disease who suffered both ischaemic and haemorrhagic lesions (1/26, 3.8%).

Eleven boys (11/26, 42.3%) and 15 girls (15/26, 57.7%) suffered from strokes. Four boys and 11 girls had ischaemic strokes while 6 boys and 4 girls had haemorrhagic strokes. The gender disparity for ischaemic strokes was not found to be statistically significant. There were 19 Chinese (19/26, 73.1%), 3 Malay (3/26, 11.5%), 2 Indian (2/15, 7.7%), 1 Eurasian (1/26, 3.8%) and 1 Caucasian (1/26, 3.8%) patients.

The median age for children with ischaemic strokes was 6.0 years (range, 3 months to 17 years) while that for haemorrhagic strokes was 8.0 years (range, 3 months to 18 years). The difference in age of onset between the 2 lesion types was not found to be statistically significant.

Clinical Presentation

Affected children most commonly presented with seizures (15/26, 57.7%), lethargy (11/26, 42.3%), hemiparesis (10/26, 38.5%), altered levels of consciousness (10/26, 38.5%), headache (10/26, 38.5%) and visual disturbances (10/26, 38.5%). Two children (2/26, 7.7%) (Table 1) who presented with convulsions also had a history of global developmental delay. They were later found to have multiple infarcts of varying ages.

History at Admission

Of the 15 children with ischaemic strokes, 6 (6/15, 40%) presented to hospital within 6 hours of onset of symptoms while the majority (9/15, 60%) presented after 6 hours.

There was no significant family history or anticoagulant use in any of our patients.

Table 1. Clinical Presentation of Strokes at Presentation

Symptom	Number	Percentage (%) of total	*P* value
Lethargy	11	42.3	<0.001
Poor feeding	1	3.8	0.327
Headache	10	38.5	0.01
Hemiparesis	10	38.5	0.01
Seizures	15	57.7	<0.001
Ataxia	4	15.4	0.43
Altered consciousness	10	38.5	0.01
Dysphasia	5	19.2	0.02
Developmental delay	2	7.7	0.16
Choreoathetosis	1	3.8	0.33
Visual disturbances	10	38.5	0.001
Complete blindness	1	3.8	0.33
Hemianopia	1	3.8	0.33
Hyperreflexia	9	34.6	0.001

Stroke Localisation

Strokes were unilateral in 15 children (15/26, 58.7%) and bilateral in 10 children (10/26, 38.5%). Ten children (10/26, 38.5%) had solitary lesions while 15 (15/26, 58.7%) had multiple lesions. Cortical strokes occurred in 14 children (14/26, 53.8%) compared to 8 children with subcortical involvement (8/26, 30.8%); 4 children had strokes in both areas.

Two children (2/10, 20%) had subarachnoid haemorrhages, 3 (3/10, 30%) had subdural haemorrhages, 9 children (9/10, 90%) had intraparenchymal haemorrhages and 3 (3/10, 30%) had intraventricular involvement.

Aetiology

An underlying aetiology was identified in 23 children (88.5%) (Table 2). Vascular abnormalities (13/26, 50%) were an important cause of both ischaemic and haemorrhagic strokes. Seven of the 10 children who suffered haemorrhagic strokes had a known risk factor diagnosed such as vitamin K deficiency or leukaemia resulting in coagulopathy.

Outcome Measures

Length of hospital stay: One non-Singaporean child was seen in the outpatient clinic only. Information concerning length of stay was not available for 3 other children. The

Table 2. Extensive Screening with Neuroimaging and Various Laboratory Investigations Identified Majority (88.5%) of Aetiologies of Childhood Stroke

Ischaemic stroke		**Number**	**% of total**
Vascular	Moyamoya disease	1	3.8
	Vertebral artery stenosis	1	3.8
	Vasculitis	1	3.8
	Vertebral artery dissection	1	3.8
	Factor V Leiden heterozygote mutant	1	3.8
	Acute lymphoblastic leukaemia (ALL)	1	3.8
Collagen vascular disease	Systemic lupus erythematosus (SLE)	3	11.5
	Antiphospholipid syndrome (APS)	2	7.7
CNS infections	Meningitis	1	3.8
Metabolic disorder	MELAS	2	7.7
Cardiothromboembolic disease	Post-cardiac surgery	1	3.8
Haemorrhagic Stroke			
Bleeding diasthesis	Vitamin K deficiency	1	3.8
Vascular	Arteriovenous malformation	3	11.5
	Acute lymphoblastic leukaemia (ALL)	2	7.7
	Congenital cyanotic heart disease	1	3.8
Both Ischaemic and Haemorrhagic Stroke			
	Moyamoya disease	1	3.8
Unknown		3	11.5

mean length of hospital stay for the remaining 22 children was 21.0 days with a median of 12.0 days (range, 4 to 75 days). The difference in mean length of stay between the 2 types of strokes was not found to be significant.

Clinical state at discharge: Of the 25 inpatients, 16 children (16/25, 64.0%) had neurological deficits at discharge – most commonly hemiparesis (12/25, 48%), followed by visual disturbances (5/25, 20%), seizures (4/25, 16%), speech difficulties (4/25, 16%), ataxia (3/25, 12%) and swallowing difficulties (3/25, 12%).

Follow-up and recovery: The average length of follow-up was 33.2 months (range, 1 to 120). Only 11 children (11/26, 42.3%) attained full recovery over a mean duration of 8.3 months (range, 1 month to 2 years). Five children recovered within a month of discharge. Full recovery occurred mostly in children with vascular (5/11, 45.5%) and collagen vascular diseases (4/11, 36.4%).

Developmental delay: Two boys who suffered ischaemic strokes at 3 months and 1 year of age, respectively, continued to have developmental delay while another 2 who suffered haemorrhagic strokes attained age-appropriate milestones at the time of review. The small sample size precluded testing for significance. Site of brain involvement did not relate to subsequent developmental delay.

Long-term outcomes: Twenty three children older than 1 year of age were assessed for long-term outcome. Three children did not have proper follow-up. There were no deaths directly resulting from strokes in our study population.

The majority of children were asymptomatic at follow-up. Two children (2/20, 10%) had significant neurological impairment,[12] while 6 (6/20, 30%) had mild functional handicap. Severe neuropsychological problems were detected in 2 children (2/17, 11.8%) at follow-up and 2 children (2/17, 11.8%) had mild schooling difficulties. Based on assessment with the modified Rankin scale for independence, 1 child (1/13, 7.7%) had moderately severe disability and required significant assistance with activities of daily living (grade 4 disability), while another child (1/13, 7.7%) required some assistance managing personal affairs (grade 3 disability) (Table 3).

Recurrence

One child (1/26, 3.8%) in our study population, who had Moyamoya disease, presented with her second ischaemic stroke at 17 years of age. Her first ischaemic stroke occurred

Table 3. Outcome Measures of Childhood Stroke Included Neurological and Neuropsychological Evaluation, Developmental Assessment and Assessment of Disability by Modified Rankin Scale

Outcome measure	**Frequency (total)**	**% of total**	***P* values**
Motor sequelae	9 (20)	45	<0.001
Cognitive impairment	4 (18)	22.2	0.02
Speech difficulties	3 (19)	15.8	0.02
Epilepsy	5 (12)	41.6	0.01
Behavioural disturbances	1 (26)	3.8	0.33

Table 4. Prognostic Factors of Childhood Stroke Included a Variety of Presenting Features and Aetiological Factors Correlated with Neuropsychological and Disability Outcomes

Prognostic factor	**Outcome measure**	***P* value**	**Odds ratio**
Altered consciousness at presentation	Cognitive sequelae	0.03	2.9
Seizures at presentation	Neurological outcome	0.02	2.1
	Neuropsychological outcome	0.01	2.7
	Motor sequelae	0.01	4.1
	Cognitive impairment	0.02	2.7
	Speech difficulties	0.03	2.4
Cortical & subcortical involvement	Cognitive impairment	0.02	3.5
Systemic disease	Neuropsychological outcome	0.03	2.7
Neurological deficits at discharge	Neurological outcome	0.01	4.4
	Neuropsychological outcome	0.01	3.7
	Absence of full recovery	0.02	4.2
	Increased length of time for full recovery	0.01	4.0
	Motor sequelae	0.03	3.0
Seizures at discharge	Neuropsychological outcome	0.04	2.0
	Rankin scale for independence	0.01	1.9

when she was 2 years old but details of her first hospital admission were unavailable.

Factors Affecting Outcomes

Clinical presentation: The presence of altered consciousness at presentation was associated with the development of cognitive sequelae such as intellectual impairment (Table 4). A significant proportion of children presenting with seizures had poor neurological and neuropsychological outcomes, increased motor sequelae, cognitive impairment and speech difficulties.

Lesion characteristics: Children who had lesions in both cortical and subcortical regions had significantly more cognitive sequelae (Table 4). Outcome was not significantly related to laterality and number of lesions.

Risk factors: Children with systemic disease had worse neuropsychological outcomes (Table 4). However, no association was found between children with multiple risk factors and poor outcomes.

Clinical state at discharge: Children who had seizures or neurological deficits at the time of discharge had significantly poorer neurological and neuropsychological outcomes (Table 4). Neurological deficits were also related to absence of full recovery, increased length of time for full recovery and persistence of motor sequelae. Age and length of time between symptom onset and treatment were not found to be related to long-term outcomes.

Discussion

Paediatric strokes are rare. Our 5-year retrospective review revealed only 26 cases of ischaemic and haemorrhagic strokes. However, as this study was limited to only one paediatric unit in Singapore, the incidence of stroke cannot be extrapolated to the whole population.

Early presentation within 6 hours of onset allows for administration of thrombolytic therapy which has been highly successful in adult strokes.[16] It was thus proposed that this might also be useful in children suffering ischaemic infarcts. However, we found that more than 50% of children who suffered ischaemic strokes presented after 6 hours of becoming symptomatic. Gabis et al[17] reported that the period of symptom onset to medical contact is often greater than 28 hours. Late presentation, related to delayed symptom recognition by caregivers as well as misdiagnosis, contributes to delay in administering appropriate treatment.[18] Although the safety of thrombolytic therapy in children has not been evaluated, early diagnosis is still important for appropriate management of intracranial pressure and other associated complications.

Hogan et al[8] concluded that cognitive outcome was worse in patients who had lesions involving both cortical and subcortical regions, but commented that this was likely related to the lesion size as well. This concurred with the findings from this study, suggesting that the management of complications of stroke is of primary importance in patients with large and extensive lesions.

Arteriovenous malformations (AVM) made up a significant proportion of haemorrhagic strokes in our study (43%). This is in keeping with a study by Meyer-Heim and Bolthauser[18] that showed an incidence of AVM of 47% in a series of cases of intracerebral haemorrhage. Of the 3 adolescents in our study who had AVMs, 1 had residual motor deficits and another had difficulties in school as well as epilepsy, demonstrating the significant morbidity from such lesions. There was no mortality in this group.

The children with ischaemic strokes in our study had well-established risk factors such as vascular arteriopathies (15.4%), collagen vascular disorders (33.3%), metabolic disorders (26.7%), infections (6.7%) and cardiac surgery (6.7%).[19-21] The high prevalence of vascular diseases was also reported in Hong Kong Chinese children with strokes.[22] There were no cases of sickle cell anaemia in the Hong Kong Chinese[22] or our study population, which is consistent with the low incidence of this disease in the Asian population. Lanthier et al[19] also found multiple risk factors in 24% of children suffering ischaemic strokes and suggested that this was associated with poor outcomes. This study found a similar proportion (26.7%) of children with ischaemic strokes who had more than 1 risk factor. However, the presence of multiple risk factors in our study population was not significantly linked to poor outcomes, which is supported by findings from the Swiss Neuropaediatric Stroke Registry.[9]

Children with systemic disease in our study were found to have significantly worse neuropsychological outcomes, comparable to other reports.[23] Interestingly, age at onset was not significantly related to a poor outcome in our study, a finding which is corroborated by Delsing et al[10] and contradicts the study by Ganesan et al.[24] The latter study excluded cases of mortality which occurred soon after stroke.

Altered level of consciousness and seizures at presentation were associated with increased intellectual impairment, which concurs with other reports.[22,25,26] Similarly, we found that children who developed epilepsy had poorer neuropsychological outcomes. This is not surprising as epilepsy may be an indicator of significant parenchymal damage from the stroke. The presence of neurological deficits at the time of discharge was also found to be a poor prognostic factor.

During our mean follow-up period of 33.2 months, only 42.3% of children had full recovery. Other studies showed varying recovery rates of 25% to 58%.[4,5,10,27,28] This low rate of full recovery may be attributed to a relatively short period of follow-up. However, Steinlin et al[9] found no

difference between neurological outcomes measured at 6 and 24 months in children who suffered strokes and further follow-up of these patients may confirm this observation.

There was only 1 recurrence (3.8%) in our study population, in a patient with Moya-moya disease. The Canadian Paediatric Ischemic Stroke Registry[28] reported similar recurrence rates of 3% to 5% while other studies observed higher rates ranging from 6% to 40%.[5,20,29,30] While secondary prevention strategies such as aspirin and thrombolytics are often used, low recurrence may suggest that in the absence of vasculopathy or thrombotic risk factors, such treatment may not benefit the large majority of patients.

Forty-five per cent of children in our study had residual motor deficits while 22.2% suffered cognitive sequelae requiring assisted schooling arrangements involving special education and learning support programmes. This emphasises the impact of stroke as a cause of long-standing childhood disability. While the study population was small, nonetheless the findings from this study underline the significant morbidity of childhood strokes, and the importance of having a high index of suspicion so as to ensure early diagnosis, access to 24-hour neuroimaging facilities, dedicated and specialised acute care for managing intracranial pressures and seizures and seamless and coordinated rehabilitative facilities to maximise outcome in such children.

Conclusion

Paediatric strokes are uncommon conditions with varied aetiologies and risk factors differing significantly from strokes suffered in adulthood. Children who suffer strokes generally have better outcomes than adults but long-term neurological, neuropsychological and functional impairment are common. Significant prognostic factors found in our study include altered consciousness and seizures at presentation, lesions in both cortical and subcortical locations, presence of systemic diseases, neurological deficits at discharge and seizures at the time of discharge. Strategies to improve outcome should therefore focus on minimising complications in patients with the above risk factors.

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