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Original Research Article

A study of risk factors and clinical outcome of stroke in children

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ABSTRACT

Background: Stroke is a significant cause of neurological morbidity and mortality in children. Early recognition permits timely therapeutic intervention aimed at preventing recurrence and improving long-term outcome. The objective of this study was to determine the risk factors, clinical outcome of stroke in children and to evaluate any association between them.
Methods: This was a prospective, observational study, conducted over one and a half year at a tertiary care centre. Children between 1 month to 12 years and diagnosed to have stroke were enrolled. The clinical profile, investigations and outcome of stroke were studied. Data collected was analysed using Pearson chi-square test.
Results: Of 55 children enrolled, definite etiology could be determined in 44 (80%) children. The common risk factors identified were vasculitis (30.9%), vasculopathy (23.6%), hypercoagulable states (18.1%), cardiac diseases (12.7%) and bleeding diathesis (7.2%). Focal neurologic deficits (69%), convulsions (58%), altered sensorium (41.8%), fever (45.4%) and aphasia (34.5%) were the chief presenting features. The overall mortality was 30.9% and neurologic deficits were observed in 54.5%. Children with undetermined etiology had a favorable outcome compared to those with definite etiology (p=0.007). Poor outcome was witnessed with vasculitis and cardiac diseases; recurrence was common with Moyamoya disease. Presence of either of altered sensorium (p=0.0005) or convulsions (p=0.046) or visual complaints (p=0.032) or headache (p=0.042) were associated with poor outcome whereas presence of focal neurologic deficits alone predicted a better outcome (p=0.036).
Conclusions: The nature of risk factor and the clinical presentation significantly influence the outcome of stroke in children.

Keywords: Children, Ischemic, Outcome, Risk factors, Stroke

INTRODUCTION

Cerebrovascular stroke is defined as sudden occlusion or rupture of cerebral arteries or veins resulting in focal cerebral damage and clinical neurologic deficit.[1] In the hospital based studies from India, pediatric strokes have constituted less than 1% of all pediatric admissions.[2,3] The incidence of arterial ischemic stroke is approximately 5 in 100,000 children per year.[4] It is being increasingly recognized as a significant cause of morbidity and mortality in children with significant social and economic consequences. There is a wide range of risk factors across age groups and across the world presumed to cause stroke. Most survivors of childhood stroke suffer neurological morbidity in form of moderate to severe neurological deficits, epilepsy in later life and recurrences. The benefits of advances in management of stroke seen in adults are not proportionately reflected in

children, probably due to paucity of research studies on childhood stroke. There is a great paucity of research studies on childhood stroke in developing countries; most studies are from developed countries. Authors intended to conduct this study with an objective to identify the risk factors of stroke in children, determine the outcome of stroke and to evaluate any association between them.

METHODS

This unicentric, prospective, observational study was carried out over a period of 18 months from January 2014 to June 2015. An approval for the study was obtained from the institutional ethics committee. The study included children aged 1 month to 12 years who presented with stroke which was defined as a sudden onset of focal neurologic deficit lasting for more than 24 hours along with evidence of an infarct on neuroimaging (CT / MRI Scan). The children with transient ischemic attack and congenital hemiplegia were excluded.

Data was obtained by interviewing the parents and/or child. Patients were called at the end of three months and outcome was noted. The clinical details, laboratory and radiological data of each patient was obtained, recorded and reviewed. The etiological work up of stroke in form of CBC, hemoglobin electrophoresis, lipid profile, coagulation profile, 2d echo and prothrombotic work up (protein C, protein S, antithrombin III levels, Lieden mutation) was done in all subjects. CSF study, immunologic and metabolic profiles were done as per clinical suspicion.

The etiologies of ischemic stroke identified in each patient were classified into different categories viz vasculitis, vasculopathy, cardiac disease, hypercoagulability and metabolic. The etiology of hemorrhagic stroke was classified as vascular anomalies, hematologic and tumors. The clinical outcome was noted at discharge and three months later at follow up. The outcome of patient at the time of follow up visit was classified as recovery /recurrence / death / persistent motor deficit / residual epilepsy / motor deficit combined with epilepsy. Data collected was analyzed using statistical tests namely Pearson chi-square test and Fisher's exact test. $P<0.05$ was kept as significant for all the statistical analysis.

RESULTS

Demographics

A total of 70 children with acute focal neurologic deficit/s were seen of which 15 were excluded in view of normal neuroimaging. Hence, 55 subjects (30 males,25 females) were enrolled, out of which 49 children (89%) had ischemic and 6 (11%) had hemorrhagic stroke. The mean age at presentation was (4.8year±SD of 3.1) with majority of the children being above 5years of age (45.5%).

The common presenting features of stroke were focal neurologic deficits (69 %), seizures (58.2%) and altered sensorium (41.2%). Of those who presented with focal neurologic deficit, 17 (30.9%) also had cranial nerve deficit, mainly seventh nerve palsy. Comparing the presenting symptoms of ischemic versus hemorrhagic stroke, it was observed that headache (4 of 6 patients, 66.6%) and visual deficit (3 of 6, 50%) were more frequently seen with hemorrhagic stroke as compared to AIS; the association between them was statistically significant ($p =0.008$ and p value=0.009 respectively).

Risk factors identified

In the present study, risk factors were identified in 44 (80%) children, of which 8 (14.5%) had multiple risk factors mainly in the form of hypercoagulability co-existent with other risk factors. Risk factors could not be identified in 11 (20%) children all of whom had ischemic stroke. All children with hemorrhagic stroke had a well-defined etiology.

The risk factors identified amongst all the children with stroke were vasculitis (17 out of 55,30.9%), vasculopathy (13 out of 55, 23.6%), hypercoagulable states (10 out of 55, 18.1%) and cardiac disease (7 out of 55,12.7%) (Table 1).

Vasculitis was mainly secondary to infectious etiology predominantly being tubercular meningitis (88.2%). Vasculopathy was mainly due to moyamoya disease (61.5%) and two children had vasculopathy secondary to varicella infection. Among hypercoagulable states, protein C and S deficiency were most common. Amongst cardiac conditions predisposing to stroke, the most common was cyanotic congenital heart disease (4 of 7). Infective endocarditis with bicuspid aortic valve, dilated cardiomyopathy with thrombus and left atrial myxoma was present in three other children. Prothrombotic states were seen coexisting mainly with congenital heart disease, moyamoya and vasculitis. The type of stroke observed with these above risk factors was ischemic type of stroke. Whereas in children with hemorrhagic stroke, three children were diagnosed to have aplastic anemia and in remaining three children, one each had hemophilia, arteriovenous malformation and intracranial tumor with hemorrhagic infarct.

Outcome of stroke

The overall mortality of stroke in present study was 31%. Mortality was high with cardiac diseases (57.1%), hypercoagulability (40%), vasculitis (31.3%) and vasculopathy (30.8%). At three months' follow up, thirty patients (54.5%) had neurological deficits, four children (7.3%) had complete recovery and four (7.3%) patients had recurrent stroke in form of new onset weakness with new infarct on neuroimaging.

The deficits chiefly observed were residual epilepsy (13 of 55, 23.6 %), motor deficit (9 of 55,16.4%) and both (8 of 55,14.5 %).The neurologic deficits were more seen in children with vasculitis (68.7%) and vasculopathy (53.8%); less seen with hypercoagulability (50%) and cardiac disease (42.8%). Recurrence was seen in children with vasculopathy (15.4%) and children with hypercoagulability (10%).

Table 1: Distribution of risk factors of stroke in present study (n= 55) few children had multiple risk factors.

Type of stroke	Etiological group	Specific etiology	Number of children
Ischemic	Vasculitis (17)	Infectious (TBM)	15
		Retroviral disease	1
		Nonspecific vasculitis	1
	Vasculopathy (13)	Moyamoya disease	8
		Post varicella	2
		Tumor vasculopathy	3
	Hypercoagulability (10)	Sickle cell anaemia	1
		Dehydration and polycythaemia	2
		Prothrombotic states with comorbid conditions	6
		Haematological malignancy (AML)	1
	Cardiac disease (7)	Cyanotic CHD	4
		Infective endocarditis with bicuspid aortic valve	1
		Dilated cardiomyopathy with intracardiac thrombus	1
		Atrial myxoma	1
	Metabolic	Melas	2
	Undetermined		11
Haemorrhagic	Hematologic and coagulopathy (4)	Aplastic anaemia	3
		Haemophilia	1
	Vascular anomaly		1
	Tumour		1

Table 2: Outcome of stroke with respect to clinical presentation.

Clinical presentation		Outcome						
		Recovery (n=4)	Recurrence (n=4)	Death (n=17)	Neurological deficit (n=30)	Total (n=55)	P value	Association
Convulsion	Yes	1	1	14	16	32	0.046	Significant
	No	3	3	3	14	23		
FND	Yes	3	4	7	23	37	0.036	Significant
	No	1	0	10	7	18		
Altered sensorium	Yes	0	1	14	8	23	0.0005	Significant
	No	4	3	3	22	32		
Visual complaint	Yes	0	0	6	2	8	0.032	Significant
	No	4	4	11	28	47		
Aphasia	Yes	1	1	10	7	19	0.092	Not significant
	No	3	3	7	23	36		
Fever	Yes	1	1	10	13	25	0.452	Not significant
	No	3	3	7	17	30		
Headache	Yes	1	0	8	4	13	0.042	Significant
	No	3	4	9	26	42		

Factors influencing outcome of stroke

Authors also attempted to study various parameters which may influence the outcome of stroke in children. The association between age and outcome of stroke was statistically not significant ($p > 0.05$). Likewise, the type of stroke; ischemic versus hemorrhagic also did not influence the outcome of stroke ($p = 0.248$).

There was no mortality in children with undetermined risk factors. Recovery too was much better seen in children with undetermined risk factors as compared to those with determined risk factors (27.3% versus 2.3%).Thus the overall outcome was better in stroke with undetermined risk factor than that with determined risk factors; the association between the two was statistically significant (p=0.007). The rate of recurrence was higher (12.5%) in those with multiple risk factors as compared to 5.6% of those with single risk factor. However, association between outcome and the number of risk factors(single/multiple) was statistically not significant. (p= 0.873).

It was even observed that mortality was higher with visual complaints (75%), headache (61.5%), altered sensorium (60.9%), convulsion (43.8%) and least with focal neurologic deficits (18.4 %). Thus, presence of convulsions, altered sensorium, visual deficit and headache at presentation were strongly associated with poor outcome (p value 0.046, 0.0005, 0.032, 0.042 respectively). Recovery was far better seen in children presenting predominantly only with focal neurologic deficit (p = 0.036) (Table 2).

DISCUSSION

Childhood stroke is a neurological condition that is associated with varied risk factors and a significant morbidity and mortality. Over 100 risk factors for stroke in children have been reported; however, the extent of the evaluation is often limited and yet no risk factors are identified in one third to one quarter of cases.[5] In the current study, 80% of children had an identifiable risk factor(s) of stroke whereas 20% children had idiopathic stroke wherein no risk factor could be identified. All these children with idiopathic stroke had an ischemic type of stroke. However, etiology could be identified in all the children with hemorrhagic stroke. Our results were similar to those recent studies conducted by Williams and Mancini et.al in which no etiology was found in 20% to 36% of patients with ischemic stroke and in 11% of patients with hemorrhagic stroke.[6-8] In a large international pediatric stroke study (IPSS) conducted by Mackay MT et al, enrolling 676 children, no risk factor was found in 9% patients.[9] The previous literature has also reported that more than a third of patients have idiopathic or unexplained stroke.[10]

The common risk factors of AIS identified in the present study were vasculitis, vasculopathy, hyper coagulopathy and cardiac disease whereas common risk factors of hemorrhagic stroke were bleeding diathesis, vascular anomaly and intracranial tumor. Vasculitis as an underlying risk factor for stroke was seen in 17 (31%) children of which, most (88.2%) were secondary to infective etiology predominantly tuberculous meningitis. Studies in Northern India conducted by Kalita J et al, and in Saudi Arabia by Salih MA et al, also reported infectious etiologies to be the most common risk factor for stroke.[11,12] There is a pattern difference in the risk factors of stroke in developed and developing countries; infectious etiology being more commonly seen in developing countries. Stroke due to vasculopathy was mainly due to Moyamoya disease (15%) which was comparable to the study conducted by Lee YY et al, in Taiwan where 13% cases had stroke due to Moyamoya vasculopathy. Cardiac diseases have also been reported to be an important cause of ischemic stroke in children next to vasculitis and vasculopathy, though in varying proportions in various countries.[13] Major cardiac risk factors include congenital heart disease especially cyanotic heart disease, acquired heart disease and patent foramen ovale.[9] Stroke is more common among children with uncorrected congenital heart disease.[14] In previous reports up to 15 % of ischemic stroke were attributed to congenital heart disease, most frequently to cyanotic CHD.[6,15,16] CHD tend to cause stroke during first four years of life. Moyamoya disease and polycythemia often coexist with cardiac disease as risk factor for stroke. The etiologic distribution of stroke in present study demonstrated different patterns compared to those with other countries. In the most recent report of international pediatric stroke study of 676 children by Mackay, the risk factors included arteriopathies (53%), cardiac disorders (31%), and infection (24%).[9] In a study conducted by Lee EH et al, in Korea, the risk factors included vasculopathy (35.5%), cardiac disease (17.4%), metabolic (14.5%), infection (14.5%) and coagulopathy (1.6%).[17]

Risk factors of stroke are even age dependent. The prevalence of various risk factors vary by age group; arteriopathy was most common in children aged 5 to 9 years in IPSS.[9] Similarly in present study , vasculopathy was commoner in older children, more than 5 years (28%) while cardiac cause was more common in infants (28.6%) compared to older children. But the association between risk factor and age was not found to be statistically significant in present study. The clinical profile varied according to the type of stroke. It was found that headache and visual deficits were more frequently seen with hemorrhagic stroke compared to ischemic stroke; the association was statistically significant (p=0.008 and 0.009 respectively).

The outcome of children after stroke varies among studies due to differences in follow-up time, functional measures, stroke type, and population studied. More than 50% of survivors develop some neurologic or cognitive problem, and 5% to 20% of affected children die.[18] Compared with ischemic stroke, hemorrhagic stroke is associated with an increased mortality. The overall mortality of childhood stroke in present study was 31%. Children with hemorrhagic stroke had almost double the mortality rates as compared to ischemic stroke At three months' follow up, more than half the patients (54.5%) had neurologic deficits in form of seizures, motor deficits alone or both which were comparable to other study Neurologic deficits were seen about three times more common in children with ischemic stroke compared to

those with hemorrhagic stroke, possibly due to more survivors of ischemic stroke and higher mortality in hemorrhagic stroke.[19] In a prospective study on 50 children conducted by Parakh M et al, in western Rajasthan, India it was found that 66 % (33 out of 50) patients has neurologic deficit at the time of discharge.[19] In a prospective cohort study conducted by de Veber GA et al, it was found that, out of 163 children who survived ischemic stroke, more than 40% had persistent moderate to severe neurologic deficits.[20] In present study only 7.3% recovered fully without any residual deficits. In a study conducted by Parakh M et al, in western Rajasthan, India recovery was seen in 24% children with ischemic stroke as compared to 33% of children with hemorrhagic stroke.[19] Recurrence of stroke was observed in 6.6% of the children in the present study as new onset motor deficit/s with fresh infarcts on neuroimaging which was thrice more common in hemorrhagic stroke than ischemic stroke. A study of combined data from Germany, Canada, and the United Kingdom of 565 patients with AIS revealed a recurrence rate of 10% after several years of follow-up.[21] Less recurrence rate in present study as compared to other studies was probably due to shorter duration of follow up.

Correlating age with outcome, it was found that rates of recovery and recurrence were almost equal in older children (>5 years) and younger children (<5years). Mortalities too were equally distributed in children between 1-5 years and >5 years of age (47.1% each). The association between outcome and age was not statistically significant (p>0.05). In a previous study by Lynch, children with stroke of undetermined etiology had a better prognosis compared to those with determined etiology.[18] Similar findings were observed in present study also. None of the patients with stroke of undetermined etiology died. Also, complete recovery was seen in three out of eleven children with undetermined etiology compared to only one of forty-four with determined etiology. The association between them was statistically significant. (p = 0.007).

Correlating outcome with individual risk factors of stroke, authors found that recurrence was more common in those with vasculopathy due to Moyamoya disease, which was also demonstrated in a study conducted in 2006 by Ganesan V et al, Two of four children who had a recurrent stroke had moyamoya disease.[22] One of these also had hypercoagulability as an additional risk factor. A prospective study conducted by Strater R et al, showed that a vascular origin and protein C deficiency was the risk factor for recurrence.[23] Kim SK et al, have demonstrated that young patients with moyamoya disease have rapid disease progression and poor clinical outcome.[24] In a Korean study conducted by Lee EH et al, it was found that cardiac disease was associated with poor outcome.[17] In present study also, risk factors predominantly cardiac diseases followed by hypercoagulability, vasculopathy and vasculitis were associated with high mortality, children with multiple risk factors have more chances of recurrence compared to those with single risk factor. In present study, recurrence was seen in 12.5% of children with multiple risk factors as compared to 5.6% in children with single risk factor though the association between the two was statistically not significant (p = 0.7). Similarly, a study conducted by Lanthier S et al, also observed that the presence of multiple risk factors was associated with higher risk of recurrence.[25]

The chances of complete recovery were comparatively less in those presenting with convulsions, altered sensorium and headache than in those presenting only with focal neurologic deficits. Death rates were the highest in children presenting with visual complaints followed by those presenting with headache; lesser in children presenting with altered sensorium and/or convulsions and least with those presenting with focal neurologic deficits alone. Thus, children presenting with only focal neurologic deficits relatively have a better outcome (p = 0.003).

To summarize, it was found from present study that risk factors identified in childhood stroke are commonly multiple and these appear to vary according to age and geographic region. Also, that presence of definite or indefinite etiology and the nature of presenting features play a significant role in determining the outcome of stroke. It is essential to entirely investigate children with stroke to look for all possible risk factors. Present study had a small sample size and short follow up, larger studies are required to provide conclusive evidence of presumptive risk factors and to detect association of risk factors with outcome.

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