

ACUTE CHILDHOOD ISCHEMIC STROKE: A PAKISTANI TERTIARY CARE HOSPITAL EXPERIENCE

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ABSTRACT

Background: Stroke in pediatric population is increasingly recognized and has diverse clinical presentation and risk factor profile. Majority of patients survive acute stroke but remain disabled. The reported literature on the subject from our part of world is scarce. **Methods:** A retrospective chart review was carried out for stroke patients between 1 month and 14 years of age, admitted between January 2009 and January 2015. Their demographic, clinical and radiological data was collected and analyzed. **Results:** Twenty nine patients were admitted with stroke over 5 years. Their mean age was 5.7 ± 11.7 and male to female ratio was 3:1. The most common clinical features reported were seizures (72%), paresis (62%), and altered mental status (52%) followed by fever (38%), cranial nerve palsies (34%) and vomiting (35%). Cardiovascular diseases (28%) were the most common identifiable etiologic factors. Only 59% had unilateral strokes. Fifty five percent had anterior circulation strokes, 14% had posterior circulation strokes while 31% had involvement of both vascular territories. Only 31% had single vessel strokes. Twenty-eight percent of the patient died during the hospital stay (mean stay was 7 ± 5 days). 62% of the infants compared to 18% of older kids ($p=0.01$), 62% of patients with both vascular territories compared 15% in single territory ($p=0.03$) and 58% of patients with bilateral strokes compared to 6% in unilateral strokes ($p=0.03$) died. **Conclusions:** Cardiovascular diseases are most common etiologic factors of stroke in pediatric age group and it carries high acute mortality. Bilateral and multiple territorial strokes, and age less than one year were associated with acute mortality.

KEY WORDS: Pediatric stroke, outcome, Imaging

INTRODUCTION

Stroke is debilitating disease which has been increasingly recognized in children in recent years, but diagnosis and management can be difficult because of the diversity of underlying risk factors and the absence of a uniform treatment approach.¹ The incidence of ischemic stroke in USA ranges from 0.56 to 2.4 per 100,000 children per year.⁴ In the Paediatric population, ischemic stroke occurs in 55% of all strokes, the rest being hemorrhagic^{4, 5}. In Contrary to adults in whom ischemic stroke comprises 80% to 85% of all the strokes cases.^{4, 5} Though hemiplegia is most common clinical presentation in pediatric stroke as in adults but seizures and fever are more common in pediatric strokes which affecting 27% and 23% respectively of pediatric stroke patient.⁶ Even when stroke presents acutely, delay in diagnosis is common, limiting the opportunities for timely interventions to improve outcome.⁴ Thrombolysis is standard of care for acute ischemic stroke in adult patients which is to be given within 4.5 hours of stroke onset⁷. Though the

experience of thrombolysis in pediatric stroke is limited but it has to be given early⁸. However, it has been reported that in about 1/3 of children with stroke present for medical evaluation within 6 hours of symptom onset^{9, 10}. Risk factor profile of stroke is distinct from adult stroke and is more diverse too. These include CNS infections, cardiac diseases (congenital and acquired) vasculopathies (fibromuscular dysplasia and moyamoya disease), vsculitidis, sickle cell disease, coagulopathies and arterial dissection.^{1,11} In a local study CNS Infections and cardiac diseases were most common etiologic factors.¹² There is great variability in the use of antithrombotic and antiplatelet drugs after acute ischemic stroke (AIS) in children.¹³ International Pediatric Stroke group reported that of the 661 children with AIS, the acute treatment consisted of anticoagulant alone in 27%, antiplatelet therapy alone in 28%, and a combination of anticoagulation and antiplatelet therapy in 16% of patients. Anticoagulation was more likely to be used in children with dissection and cardiac disease and less likely to be used in patients with other risk factors¹³. After an episode of cerebral

ischemia, children usually show substantial improvement in the first 2 to 3 weeks and slower progress over the next several months, however, many children are left with persistent neurologic deficits.¹⁴ About 10% of children die during acute period, and among the survivors, 70% are left with neurologic deficits¹⁵ and approximately 15% to 20% have further strokes.^{16, 17} Data on pediatric stroke from Pakistan is scarce. Our objective is to describe the clinical features, management and outcome of acute ischemic stroke in pediatric patients admitted in a tertiary care university hospital in Karachi, Pakistan.

MATERIALS AND METHODS

We conducted a retrospective chart review of all cases of acute ischemic stroke, who were admitted in the pediatric ward of Aga Khan University Hospital (AKUH), Karachi, Pakistan from January 2007 till December 2012. Records were retrieved by using ICD-9 coding system through our health information management system. Patients aged below one month and above 14 years were excluded. Patients in whom imaging was not performed were also excluded. Other exclusion criteria included patients with post traumatic or post anoxic brain ischemia and with history of birth asphyxia, spinal and brain trauma, GuillanBarre syndrome, poliomyelitis, these diseases could result in seizures and other symptoms of interest on their own and that would contaminate our data. The demographic, clinical, laboratory, radiologic and pharmacologic data as well as post discharge follow up was recorded on a structured proforma. The data was analyzed on SPSS version 20.0 (IBM, Chicago, USA). Summary statistics were used to describe the cohort. Results were presented as mean and standard deviation for continuous variables and frequencies and percentage for categorical variables. The study was approved by the institutional ethics review committee.

RESULTS

We identified a total of 29 pediatric patients with acute ischemic stroke over a period of 5 years. Their mean age was 4.52 ± 4.1 years with seventy six percent over the age of one year. Male to female ratio was 3:1. Mean duration of symptoms at the time of presentation was 5.75 ± 11.73 . Seizures, loss of consciousness, paresis were the commonest clinical presentations followed by fever, vomiting, cranial nerve palsy, delayed development, headache and blindness (figure 1). Out of the 21 patients who had seizures at presentation, 13 (62%) had generalized seizures, 7 (33%) had focal and 1 (5%) had myoclonic seizures. The cause of ischemic stroke was identified in 22 patients and is shown in figure no.2. Past history of stroke were present in only 2 (7%) patients and positive family history of stroke were identified in only 1 (3.4%) patient. Echocardiogram was performed in 13 patients that

revealed myocarditis in 5, tetralogy of Fallot, complex congenital heart disease and ventricular septal defect one in each. None of these patients had patent foramen ovale. Ejection fraction was low in 4 patients (40% in one and 20-25% in 3). Prothrombotic workup was performed in 8 patients and 3 of these had hypercoagulopathy (protein S deficiency in 2 and protein C deficiency in 1). CNS infections were noted in three patients (2 meningitis, 1 encephalitis), hematologic abnormalities noted in three patients (one each had hemophagocytic lymphohistiocytosis, thalassemia major who underwent bone marrow transplant and hereditary spherocytosis), three had vasculopathies (moyamoya in one and idiopathic vasculopathy in 2), 2 had possible mitochondrial disorders and 2 had dehydration/hypovolemia. All patients underwent brain imaging (4 had only CT scan of head and 25 had either MRI brain or CT and MRI both). Anterior circulation strokes were seen in 16 (55%), posterior circulation strokes in 4 (14%) patients while in 9 (31%) patients both circulations were effected. Twelve (41%) had bilateral and 17 had (59%) unilateral strokes. Eight (28%) received anticoagulation and 20 (69%) received aspirin. Anti-seizure medications were given to 22 (76%) patients. All children received supportive treatment acutely, with some receiving physical, speech, or occupational therapy or a combination of rehabilitation modalities. Mean length of stay was 7 ± 5 days. Eight (28%) patients died during the hospital stay and 21 patients were sent home. In a univariate analysis, multiple strokes and age below one year were associated with higher mortality (Table no 1). Each of the survivor had at least two follow up visits and their mean follow up period was 15 ± 9.5 months (Range: 2-35). Four patients died during follow up while 3 patients had complete recovery, and 14 of 17 (82%) patients had residual neurologic deficit (motor, cognitive deficits or both).

DISCUSSION

This study presents a detailed report of the patients who presented to Aga Khan University Hospital with ischemic stroke during a 5 year period. Mean age of our patients was 4.5 ± 4.2 (median 3) years and there was male predominance. An Indian study reported mean age of about 11 years while international pediatric stroke study (IPSS) reported median age of about 5 years.^{13,18} Though the age of our patients was relatively younger but we noted male preponderance which has been reported by a hospital based in India and the multicenter IPSS.^{13,19} The relatively younger age group at presentation (mean 39 months) has been reported earlier from Pakistan.³ Selection bias is always a possibility in hospital based studies specially the retrospective ones but possibility of the fact that stroke in our country occurs at younger age cannot be excluded. In Pakistan adult stroke has been reported to occur about a decade earlier than that

reported from West.^{20,21} We noted that cardiac disorders (congenital or acquired) were the most common causes of stroke in our patients followed by CNS infections, hypercoagulopathies, hematological diseases and vasculopathies. This finding that is consistent with previous reports.^{1, 3, 11, 12, 18, and 22} Previous studies reported that hemiplegia was the most common clinical presentation followed by seizures in such patients.^{3, 6, 18} However; our data showed that seizures were more common manifestation followed closely by hemiplegia. One reason could be that our patient presented to the hospital early, before the onset of more advance symptoms such as hemiplegia. The treatment for ischemic strokes most commonly reported in other studies consists of anticoagulants, antiplatelets or a combination of both of these.^{13a} A similar strategy was noted in our patients, however, in IPSS anticoagulation and antiplatelet were used in almost equal number of the patients while most of our patients received antiplatelet agent. This simply reflects variations in stroke management among the treating physicians. Though there is robust evidence for specific treatment in stroke patients with sickle cell disease, moyamoya disease but for rest of patients the evidence and recommendations are of relatively low level.¹ The mortality rate among our patients in acute period (during index hospitalization; mean hospital stay was 7 ± 5 days) was 28% which is significantly higher than earlier reports which mentioned mortality below 10%.^{13,16, 17,18} Similarly, post-discharge mortality of our patients was also high i.e. 14% of the survivors died during the mean follow up period of 15 ± 9.5 days. The high mortality rate is probably multifactorial. Most of our patients had bilateral multiple strokes which has been reported as poor prognostic factor.¹³ Cardiac disorders were most common etiologic factors in our patients and these are reported to be more frequently associated with bilateral strokes.²² Young age and fever at presentation have also been reported as poor prognostic factors in long term.²³ Mean age of our patients was relatively young comparative to the age reported in literature and about 40% of our patients had fever at presentation. These might be the contributory factors to poor outcome in our patients. Additionally, lack of trained neurologists (most of pediatric stroke patients are managed by general pediatricians), lack of stroke units and lack of pediatric focused rehabilitation services, all might be contributory. Previous studies have reported that among the patients who survive after a stroke 70% has persistent neurological deficits.^{16, 17} we also noted residual neurologic deficits in 82% of the patients. Our study shows that clinical presentation, etiologic factors and prophylactic management is more or less similar to prior reported literature, however, significant differences were also noted including relatively younger age at onset, high immediate and long term mortality. The establishment of multicenter pediatric stroke database

study in Pakistan is needed to further evaluate our findings.

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Ethical approval:

The study was approved by the institutional ethical review committee No: 2817-Ped-ERC-13

Table 1: Factors associated with acute mortality

Factor	Mortality	p value
Age: ≤ 1 year vs. > 1 year	5/8 (62%) vs. 3/21 (14%)	0.019
*Ant and post circulation vs. either ant or post circulation strokes	5/9 (56%) vs. 3/20 (15%)	0.037
Bilateral vs. unilateral strokes	7/12 (58%) vs. 1/17 (6%)	0.003
Strokes in multiple arterial territories vs. single artery strokes	8/20 (40%) vs. 0/9 (0%)	0.029

*ant: anterior, post: posterior

REFERENCES

1. management of patients with acute ischemic stroke: a guideline for healthcare professionals from the American Heart Association/American Stroke Association. *Stroke* 2013; 44: 870-947.
6. Amlie-Lefond C, deVeber, Chan AK, et al Use of alteplase in childhood arterial stroke: a multicenter, observational, cohort study. *Lancet Neurol* 2009; 8: 530-6.
7. Ganesan V, Prengler M, McShane MA, et al. Investigation of risk factors in children with arterial ischemic stroke. *Ann Neurol* 2003; 53: 167-73.
8. Fullerton HJ, Wu YW, Zhao S, et al. Risk of stroke in children: ethnic and gender disparities. *Neurology* 2003; 61: 189-94.
9. Siddiqui TS, Rehman A, Ahmed B. Etiology of strokes and hemiplegia in children presenting at Ayub teaching hospital, Abbottabad. *J Ayub Med Coll Abbottabad* 2006; 18: 60-3.
10. Bowen MD, Burak CR, Barron TF. Childhood Ischemic Stroke in a Nonurban Population. *J Child Neurol* 2005; 20: 194-7.
11. Goldenberg NA, Bernard TJ, Fullerton HJ, et al: Antithrombotic treatments, outcomes, and prognostic factors in acute childhood-onset arterial ischemic stroke: A multicentre, observational, cohort study. *Lancet Neurol*

- 2009; 8: 1120-7.
12. Gordon AL, Ganessan V, Towell A, Kirkham FJ: Functional outcome following stroke in children. *J Child Neurol* 2002; 17: 429-34.
 13. Lefond CA and Gill JG. Pharmacology in Childhood Arterial Ischemic Stroke. *SeminPediatrNeurol* 2010; 17: 237-44.
 14. Fullerton HJ, Wu YW, Sidney S, et al: Risk of recurrent childhood arterial ischemic stroke in a population-based cohort: The importance of cerebrovascular imaging. *Pediatrics* 2007; 119: 495-501.
 15. Ganesan V, Prengler M, Wade A, et al. Clinical and radiological recurrence after childhood arterial ischemic stroke. *Circulation* 2006; 114: 2170-7.
 16. Kalita J, Goyal G, Misra UK. Experience of pediatric stroke from a tertiary care medical center in North India. *J NeuroSci* 2013; 325: 67-73.
 17. Golomb MR, Fullerton HJ, Nowak-Gottl U, deVeber G; for the International Pediatric Stroke Study Group. Male predominance in childhood ischemic stroke. Findings from the International pediatric stroke study. *Stroke* 2009; 40:52-7.
 18. Khealani BA, Khan M, tariq M et al. Ischemic strokes in Pakistan: observations from the national acute ischemic stroke database. *J Stroke Cerebrovasc Dis* 2014; 23: 1640-7.
 19. Mehndiratta MM, Khan M, Mehndiratta P, Wasay M. Stroke in Asia: geographical variations and temporal trends. *J NeurolNeurosurg Psychiatry* 2014; 85: 1308-12.
 20. Dowling MM, Hyman LS, Lo W et al. International pediatric stroke study: stroke associated with cardiac disorders. *IJS* 2013; Suppl A100: 39-44.
 21. Crossen MH, Aarsen FK, Akker SLVD et al. Pediatric arterial ischemic stroke: functional outcome and risk factors. *DevNeurol& Child Neurol* 2010; 52: 394-9.

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