ORIGINAL ARTICLE

Pediatric Stroke: The Clinical and Etiological Spectrum: An Observational Study from a Tertiary Care Stroke Clinic, Kolkata, India

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Abstract

Background: In different geographical regions, the clincoetiological spectrum of childhood stroke varies widely and studies from Eastern India is lacking.

Objective: To determine the clinicoetiological spectrum of childhood stroke and their outcome.

Materials and methods: This study was conducted in a stroke clinic of a tertiary care hospital of Kolkata over a period of 18 months. All children below 12 years diagnosed as stroke were included. On the basis of clinical examination, relevant laboratory investigations and radioimaging etiologies were determined. Appropriate statistical methods were used to analyze the data gathered from these patients using a preformed proforma.

Results: Among the 70 pediatric stroke patients, the most common clinical presentation was found to be hemiparesis (61.42%) followed by seizure (30.00%) and aphasia (25.71%), respectively. Vasculopathies (30.00%) were found to be the most common etiology of childhood stroke followed by infective meningoencephalitis and craniocervical trauma (14.28% each). Ischemic stroke comprised 71.4% of cases. During discharge, 20 cases (28.57%) showed complete recovery, whereas 40 cases (57.14%) had persistent neurodeficit [Pediatric Stroke Outcome Measure (PSOM) score >1], 12 cases (17.14%) had recurrent stroke, 8 cases (11.42%) died, and only 2 (2.85%) patients were lost to follow-up. Out of those 40 cases having persistent neurodeficits during discharge had recovered too at follow-up at 18th month. At presentation PSOM score in 40 cases (57.14%) was >5 and at follow-up at 18th month, only 8 cases (11.42%) had PSOM score of >5.

Conclusion: The commonest etiologies of stroke in pediatric patients presenting at our hospital were found to be intracranial vasculopathies, infection, and trauma. Ischemic stroke was the predominant type. Eighteen-month follow-up showed complete recovery from acute neurological deficits in most of the patients.

Keywords: Hemiplegia, Infections, Outcome, Pediatric stroke outcome measure, Vasculopathy.

Indian Journal of Physical Medicine & Rehabilitation (2019): 10.5005/jp-journals-10066-0058

Introduction

Stroke in the pediatric age group is an increasingly conceded cause of significant long-term morbidity that creates a substantial burden of illness on the affected individual as well as society at large.[1–3] Estimated annual incidence of childhood stroke is 1–6 per 100,000 children with 50% being the ischemic type including arterial ischemic stroke (AIS) and cerebral venous sinus thrombosis (CVT).[4–6] Incidence in neonates is even higher at 1 in 3,000 to 5,000 live births.[7–9] In 50–90% of children, neurological deficits persisted in the form of motor, language, and cognitive deficits.[10] Data regarding specific etiology and outcome of childhood stroke are sparse from the Asian countries.[11] So, this study was undertaken to determine the clinicoetiological profile and their outcome from a tertiary care stroke unit in eastern India.

Materials and Methods

This retrospective observational study was carried out in the Stroke Clinic at Department of Neuromedicine at Bangur Institute of Neurosciences, Kolkata, during the period of September 2017–March 2019 after obtaining proper informed consent from parents of the patients and ethical clearance from the institutional ethics committee.

Patients below 12 years who presented with clinical features suggestive of stroke (i.e., hemiparesis, aphasia, seizure, altered consciousness, etc.), which was later confirmed by neuroimaging,

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How to cite this article: Dubey S, Ghosh R, Chatterjee S, *et al.* Pediatric Stroke: The Clinical and Etiological Spectrum: An Observational Study from a Tertiary Care Stroke Clinic, Kolkata, India. Indian J Phys Med Rehab 2019;30(3):74–80.

Source of support: Nil

Conflict of interest: None

were included in this study. Thorough history was taken and detailed clinical examination was done on admission and recorded in a predesigned and pretested format. Complete hemogram, lipid panel, liver function tests, coagulation profile, thrombophilia profile, autoimmune profile, triple viral serologies (HIV, hepatitis B, hepatitis C), cardiac evaluation, cerebrospinal fluid analysis in some cases, high-performance liquid chromatography, computed tomography scan brain, magnetic resonance imaging (MRI) brain (3 Tesla), magnetic resonance angiography (MRA)/venography (MRV), and digital subtraction angiography (DSA) were done where indicated. All the patients were rigorously monitored during their hospital stay and then they were periodically followed up to 18 months' post-discharge.

The outcome of these children was assessed and recorded at two different time frames—at presentation and again at 18 months of follow-up, with the help of the Pediatric Stroke Outcome Measure (PSOM) scale for disability assessment in stroke, dividing into three groups—complete recovery, persistent neurodeficit, and death.[12] Pediatric Stroke Outcome Measure is a well-known scoring system widely used to assess neurological recovery in pediatric patients after stroke. It comprises five subscales: right sensorimotor, left sensorimotor (each with subcategories), language production, language comprehension, and cognitive/behavioral. A total score ranging from 0 (no deficit) to 10 (maximum deficit) is given based on the sum of the five subscale scores.

All data were collected, compiled, and subjected to analysis using Microsoft Word and Excel 2007.

Results

A total of 70 patients were included in this study out of which there were 46 males (65.71%) and 24 females (34.28%). The mean age of these patients was 6.12 ± 3.5 years and the median age was 6.5 years.

A total of 50 cases (71.42%) had AIS, 16 (22.85%) had hemorrhagic stroke, and 4 (5.71%) had CVT. Regarding the etiologies, vasculopathies were found to be the most common one (21 cases, 30%) followed by intracranial infection and head and neck trauma (10 patients, 14.28% in each group), followed by prothrombotic state (9 cases, 12.85%), cardiac (7 patients, 10%), central nervous system (CNS) vasculitis (5 cases, 7.14%), hematological [4 cases, 5.71%; 2 cases of acute lymphoblastic leukemia (ALL), 1 case of immune-mediated thrombocytopenic purpura (ITP), and 1 case due to thrombocytopenia secondary to dengue hemorrhagic fever], hypertension [2 cases, 2.85%, one due to Liddle syndrome and the other due to fibromuscular dysplasia (FMD) of renal arteries], and metabolic [2 cases, 2.85%; both due to mitochondrial encephalopathy, lactic acidosis, and stroke-like episodes (MELAS)].

Among vasculopathies, moyamoya angiopathy (MMA) topped the list with 14 cases (20% of total case pool) followed by arterioveinous malformation (AVM) (2 cases), vascular malformation associated with Down's syndrome (2 cases) and with neurofibromatosis (2 cases), and 1 case of aneurysm. Among the 14 cases of moyamoya vasculopathies, 12 cases were ischemic infarct and 2 cases had intraventricular hemorrhage.

Among CNS infections, tubercular etiology topped the list with eight cases (11.42% of total case pool) followed by one case of Japanese B encephalitis and one case of herpes simplex virus (HSV)-2 encephalitis. Amidst tubercular CNS infections, all eight cases had tubercular vasculitis, six cases had associated tubercular meningitis, and four cases had associated tubercular granuloma. Though hemiparesis was commonest presentation in infective cases, concomitant presence of headache and vomiting was found in 7 out of 10 cases.

Amidst craniocervical trauma, four (5.71% of total cases) cases presented with hemorrhagic stroke and other six (8.57% of total cases) presented with ischemic infarct (four cases of basal ganglia infarcts and two cases of large artery stroke due to dissection of carotid and vertebral artery). Out of nine cases of prothrombotic states, anti-phospholipid antibody syndrome (APLAS), factor deficiencies, and dehydration as the potential risk factors for prothrombotic state leading to AIS were found. Among four cases of CVT (three females, 1 male), one case was following ear infection, one was due to underlying secondary APLAS, one was due to probable dehydration, and one was idiopathic. Out of seven cases of cardiac causes of stroke, five (7.14%) cases were due to congenital heart diseases and two (2.86%) cases had patent foramen ovale. Out of five cases of CNS vasculitis, it was found that Kawasaki Disease, Henoch Schonlein purpura (HSP), polyarteritis nodosa (PAN), systemic lupus erythematosus (SLE), and probable primary CNS vasculitis all had singular case. Sixteen patients of hemorrhagic stroke revealed trauma being the most common (four cases, 25%) etiological burden followed by three cases (18.75%) of AVM rupture, two cases (12.50%) of hypertensive hemorrhage (one Liddle syndrome, one fibromuscular dysplasia), two cases (12.50%) of MMA, four cases (25%) bleeding diastheis, and one case (6.25%) of aneurysmal rupture. Table 1 shows the etiologic distribution of stroke across the study sample.

Hemispherical distribution revealed that in 38 cases (54.28%), left hemisphere was involved and in other 32 cases (45.71%), right hemisphere was involved. Regarding distribution of the cases according to their localization it was observed that in 33 cases (47.14%) had subcortical stroke, in 21 cases (30%) the involvement were purely cortical, and in another 10 (14.2%) cases involvement was cortical with subcortical extension or vice versa (vide Table 2). Out of 21 pure cortical strokes, 10 (47.6%) cases had MMA, 3 (14.2%) cases had CVT, 3 (14.2%) cases had cortical hemorrhage (2 bleeding diasthesis, and 1 AVM rupture), and 5 (23.8%) cases had other causes of AIS.

Hemiparesis (43 cases, 61.42%) was the most common presenting symptom of childhood stroke found in this study, followed by seizure (21 cases, 30%), aphasia (18 cases, 25.71%), headache (14 cases, 20.00%), visual impairment (7 cases, 10.00%), altered consciousness (7 cases, 10.00%), and movement disorder (3 cases, 4.28%) respectively. Interestingly, preceding febrile illness were seen 17 cases (24.28%). Of the 50 cases of AIS, 36 cases (72.00%) had hemiparesis, 14 cases (28.00%) had some form of aphasia, 15 cases (30.00%) had seizures, and 6 cases (12.00%) had visual abnormality at the time of presentation (vide Table 3). Interestingly, all the cases of CVT and 60% of the cases of acute hemorrhagic stroke and only four of the ischemic strokes (all due to MMA) presented with headache.

Regarding outcome assessment, we found that out of 70 children only 8 cases (11.42%) died, 2 cases (2.85%) were lost to subsequent follow-up, and 12 cases (17.14%) had recurrent stroke. Among the 12 cases of recurrent stroke, 8 cases were due to MMA, 2 cases were due to recurrent AVM rupture, and other 2 cases were due to MELAS. Complete recovery from neurodeficit was found in 20 cases (28.57%). Of the rest 40 patients, PSOM was <5 in 32 cases

Table 1: Distribution of pediatric stroke patients according to various etiologies

Etiologies	*Cases (%)*
1. Vasculopathies	21 (30)
(a) MMA	14 (20)
(b) Isolated AVM	2 (2.85)
(c) AVM associated with Downs	2 (2.85)
(d) AVM associated with NF-1	2 (2.85)
(e) Rupture of aneurysm	1 (1.42)
2. CNS infections	10 (14.28)
(a) TB	8 (11.42)
(b) Japanese-B encephalitis	1 (1.42)
(c) HSV-2 encephalitis	1 (1.42)
3. Craniocervical trauma	10 (14.28)
4. Prothrombotic state	9 (12.85)
(a) Primary APLAS	2 (2.85)
(b) Secondary APLAS	2 (2.85)
(c) Protein-C, S deficiency	2 (2.85)
(d) Hyperhomocysteinemia	1 (1.42)
(e) Anti-thrombin 3 deficiency	1 (1.42)
(f) Idiopathic	1 (1.42)
5. Cardiac causes	7 (10)
(a) Congenital heart diseases	5 (7.14)
(b) Patent foramen ovale	2 (2.85)
6. Vasculitis	5 (7.14)
(a) Kawasaki	1 (1.42)
(b) HSP	1 (1.42)
(c) PAN	1 (1.42)
(d) SLE	1 (1.42)
(e) Primary CNS vasculitis	1 (1.42)
7. Hematological	4 (5.71)
(a) ALL	2 (2.85)
(b) ITP	1 (1.42)
(c) Dengue hemorrhagic fever	1 (1.42)
8. Hypertension	2 (2.85)
(a) Liddle syndrome	1 (1.42)
(b) FMD of renal arteries	1 (1.42)
9. Metabolic causes	2 (2.85)
MELAS	2 (2.85)

Table 2: Distribution of stroke cases according to localization

Location	*Cases (%)*
Subcortical	33 (47.14)
Pure cortical	21 (30)
Cortical with subcortical extension	10 (14.2)

(45.71%) and PSOM was >5 in only 8 cases (11.42%) at 18 months (vide Table 4).

Discussion

Stroke in children was previously considered to be rare and frequently misdiagnosed largely owing to low level of suspicion by clinicians and the frequent subtlety of the symptoms with which

Table 3: Distribution of stroke patients according to clinical features

Clinical features	*Infarct*	*Hemorrhage*	*CVT*
Hemiparesis	36	5	2
Seizure	15	3	2
Aphasia	14	4	0
Headache	4	6	4
Visual impairment	6	0	1
Altered consciousness	4	2	1
Movement disorder	3	0	0
Preceding febrile illness	10	7	0

Table 4: Distribution of cases according to outcome at 18th month of follow-up

Outcome	*Number (%)*
Complete recovery	20 (28.57)
Persistent neurodeficit	40 (57.14)
(A) PSOM score > 5	8 (11.42)
(B) PSOM score < 5	32 (45.71)
Recurrent stroke	12 (17.14)
Death during course of study	8 (11.42)
Lost to follow-up	2 (2.85)

cases presented with and this resulted in significant long-term morbidity in these patients. A report by Braun et al.[13] showed that delay in the diagnosis of stroke in 19 out of 45 children ranged from 15 hours to as long as 3 months after initial presentation. Gabis et al.[14] also demonstrated that mean elapsed time from presenting symptom to initial imaging was a total of 35.7 hours (median: 12 hours; range: 0.1–300 hours). A mean lag of 28.5 hours (median: 5.5 hours; range: 0–240 hours) till first encounter with a healthcare provider and an extra mean delay of 7.2 hours (median: 6.6 hours; range: 0–60 hours) in getting a brain imaging done after presentation. Difficulties at levels of the parents, school personnel, or caregiver, in recognizing the graveness of various subtle symptoms, resulted in delayed healthcare contact. The initial symptom can be a common complaint, such as headache or fatigue, and the child might not complain.[14] However, studies have shown that the incidence of pediatric stroke has increased to almost double of that from the prior decades.[15] This can be ascribed to a multitude of factors such as increased survival in children with risk factors for stroke, such as congenital heart disease, sickle cell disease, and leukemia, increased awareness among clinicians and people, and greater availability of advanced diagnostic and therapeutic armories.

A few prospective and retrospective studies have been reported from Southeast Asia,[16–19] but our study differed from their outcome in several ways. In our study, 50 (71.42%) patients were of ischemic stroke and 16 (22.85%) patients were diagnosed as a hemorrhagic stroke. This may be because ours being an apex institute, most cases of hemorrhagic stroke are admitted in the neurosurgery department for necessary action and hence have been excluded from the study. Adequate identification and determination of etiology is absolutely necessary as stroke can be prevented in some children and treated in others. In our study, vasculopathies were the most common etiology (30%), MMA being the most common among them (20%). Other etiologies

in decreasing order of frequencies were intracranial infections (14.28%) followed by craniocervical arterial dissection (14.28%). Tubercular meningitis was found to be the most common infective etiology. Amlie-Lefond et al.[20] and Rosa et al.[21] in their review on pediatric stroke revealed that apparently arteriopathy was predominant underlying mechanism, causing 53% of pediatric strokes. An Asian study by Lee et al.[17] in 2008 also showed vascular etiology (33%) as commonest and intracranial infection as the second most common cause similar to our study. A study by Lee et al.[18] also showed vasculopathy (35.5%) to be the most frequent etiology behind childhood strokes as in our study. However, intracranial infection was found to be much lower down the order compared to our study. Recent study conducted in India, by Patra et al.[16] and Patil et al.,[22] found intracranial infection to be the most frequent etiology of stroke, unlike ours. A study from Pakistan by Siddiqui et al.[23] also showed intracranial infection to be the most frequent (56%) etiology of pediatric stroke. This discrepancy is probably because our institute was a highest regional tertiary care referral center and therefore there may a clustering of moyamoya and other vasculopathies. The most common etiologic factors for the ischemic stroke were protein C deficiency (9, 23.1%). The most common etiologic factor for hemorrhage was bleeding disorders in about 50% of patients.[24] Tsze et al. reported cardiac disorders as the most common etiological factor in childhood stroke accounting for almost one-third of all cases followed by hematologic and infective causes. They put vasculopathies and trauma much behind as etiological factors.[25] In a Chinese prospective study on pediatric stroke, Chung et al. also reported cardiac diseases as most common etiologic factor followed by vasculopathies.[26] Compared to the studies from Western region and many a study from the Occident, distribution of the causative factor of pediatric stroke unfurled dissimilar patterns. Cardiac diseases, sickle cell disease, and major arterial dissections were the frequent most underlying illnesses in previous reports from West,[1,27–29] whereas moyamoya vasculopathy was the most common etiology in this study. As seen in earlier Asian series, high frequency of moyamoya disease was found in this study.[17,18,26,30] The International Pediatric Stroke Study (IPSS) group analyzed 1,187 children with stroke[31] with varying ethnic composition, vasculopathies, and cardiac diseases were the predominant causes. Moyamoya disease accounted for merely 6% in this group.[31] Recent most assessment report of the IPSS for risk factors included arteriopathies (53%), cardiac disorders (31%), and infection (24%) followed by acute head and neck disorder (dissection) and acute or chronic systemic illnesses.[32]

Treatment is influenced by the etiology of stroke, especially in cases of moyamoya diseases; hence, it is necessary to establish. Patients with moyamoya disease are offered surgical intervention as definitive therapy.[33,34] Kim et al. have demonstrated a need for earliest possible surgical intervention to prevent poor outcome and rapid disease progression.[35] Therefore, especially in East Asia, moyamoya disease should always be suspected in a child presenting with sudden-onset focal neurodeficit and they should be evaluated promptly by MRA to make a certain therapeutic plan. Cardiac diseases have also been reported to be an important cause of ischemic stroke in children.[1,26,36,37] In contrast, we only had 10% of cases with a cardiac etiology behind their stroke, and were associated with poor outcomes. The frequency of cardiac diseases in this study was higher than the 6.1% reported in a previous study of Korean children.[30] This discrepant finding had three robust explanations: (1) incidence of strokes from cardiac diseases has truly declined over the last decade because of early diagnosis and treatment of the primary cardiac defect and (2) due to selection bias, (3) this was probably because of lack of availability of sophisticated tools in our setting to pick up cardiac causes of childhood stroke.

An increased risk of pediatric stroke has been seen with some inherited metabolic disorders. Many of the cases of pediatric strokes having unknown etiology actually has these disorders underneath. Treatment can be provided for these cases if correctly diagnosed.[38,39] We found two patients with stroke caused by MELAS and one with homocysteinemia. The exact mechanopathology of stroke-like episodes in MELAS is unknown. It has been thought that due to aberrant accumulation of mitochondria in vascular endothelium and smooth muscle cells, mitochondrial angiopathy occurs that leads to ischemic lesions in MELAS.[40] Other rare conditions associated with metabolism that increase the risk of stroke include organic aciduria, urea cycle disorders, and Fabry disease, but none of our patients had any of these conditions. Etiological background was shown in previous studies to be pervasively related to chances of recurrent stroke and final outcome. Patients with MMA, embolic stroke, and stroke due to systemic illness had poorer outcomes compared to patients with nonprogressive arterial disease.[36] Protein C-deficient state, elevated lipoprotein-(a) levels along with vasculopathies were associated with increased risk of stroke recurrences.[41] In the present study, the risk of recurrence was varied with cardiac disease, metabolic disorder, and vasculopathy, similarly to previous studies.

Central nervous system infections commonly manifested as ischemic stroke in our study population. Inflammatory mechanisms often coexist with infections. This can activate the coagulation cascade by several pathways, viz., increased expression of thromboplastin by monocytes and macrophages,[42] increased serum level of tumor necrosis factor which can affect pro-coagulant function of endothelium, increased levels of clotting factors like fibrinogen, or by inhibition of anticoagulation systems involving Protein C and Protein S.[42–46] Thus, we often find the mechanism of stroke in intracranial infection is often some form of vascular catastrophe.

Postvaricella angiopathy, rarely considered an important cause of pediatric ischemic stroke, often manifest weeks or months after an uncomplicated chicken pox illness.[47,48] Radioimaging features of postvaricella angiopathy include basal ganglia infarction and stenosis of various portions of circle of Willis. Postvaricella angiopathy in childhood gives rise to recurrent TIAs or strokes. However, in our study cohort we did not get any such case.

Fullerton et al. demonstrated that craniocervical arterial dissection (CCAD) in the pediatric age group usually presents with symptoms of acute ischemic stroke (AIS) or transient ischemic attack (TIA).[49] Exposure of uncovered endothelial collagen to naked von-Willebrand factor and activated tissue thromboplastin results in when intimal layers of a vessel wall gets split up due to dissection. This results in fibrin formation, platelet adhesion, and thrombus formation and propagation. Ischemia occurs due to vaso-occlusion at the site of dissection or from clot dislodgement and upstream embolus formation.[50] Aneurysmal dilatation, occurring secondary to impaired integrity of the vessel wall and persistent arterial pressure occlusion, frequently appears in the C1-C2 vertebral artery dissection in children. It is common due to aneurysmal dilatation preceded by persistent pressure occlusion and altered vessel wall integrity.[50,51] Extracranial dissection and intracranial dissection are the two types of CCADs in childhood and

have different risk factors and treatment. Almost 5–25% of ischemic-type childhood strokes are caused by extracranial dissections, often post-traumatic. Craniocervical arterial dissection was an important cause of childhood stroke in our study cohort. Four cases had basal ganglia stroke due to intracranial dissection and two cases had large artery infarct. Craniocervical arterial dissections involving anterior circulation usually present with hemiparesis, aphasia, or other focal neurodeficits. On the contrary, vertebrobasilar dissection (posterior CCADs) can present with myriad of clinical features ranging from mild disequilibrium to loss of consciousness/coma as seen in our patients. Hence, diagnosing posterior CCADs become quite defying. History of recent trauma and/or lower cranial nerves affection should be taken as clues. Early evidence suggests that posterior CCADs are more prevalent than anterior CCADs in pediatric ischemic stroke.[52] Interestingly, as observed in cases of this study, diffuse headache is more common in children with CCAD unlike in adults where neck pain is a prominent complaint.[53,54] Difficulties in establishing definitive diagnosis bar the assessment of prevalence of intracranial dissection in childhood. Intracranial transient focal cerebral arteriopathy (FCA), occurring in up to 80% of previously healthy children with AIS, has been the main focus of recent literatures.[20] Various evidences suggested that an infective or para-infectious process may be likely to cause many of these transient FCAs, rather than dissections.[20] However, CCADs are enforced to be the cause of these transient FCAs in recent literatures (Dlamini et al.).[55]

Central nervous system vasculitis, a rare cause of stroke in children, may be associated with systemic connective tissue disorders as SLE, polyarteritis nodosa, Takayasu's arteritis, juvenile rheumatoid arthritis, or inflammatory bowel disease.[56] Isolated angiitis of the central nervous system (IACNS) occurs in children either as a predominantly small vessel process or involving large arteries.[57] Leptomeningeal biopsy should be performed in suspected cases of IACNS prior to committing a child with arterial stenosis to immunosuppressant therapy. We got five cases of vasculitic infarcts. All improved significantly with immunosuppressive therapy.

On close observation of nine cases (12.85%) of prothrombotic states, we found primary APLAS (two cases), secondary APLAS (two cases), factor deficiencies (four cases), and dehydration (one case) as the potential risk factors for prothrombotic state leading to AIS. Various systemic conditions of childhood and dehydration often lead to intravascular volume depletion with increased risk of thrombogenesis. However, pediatric stroke may be linked with several thrombophilic conditions and a myriad of more serious primary or secondary hematological disorders. Platelet disorders including thrombocytosis can be associated with AIS. In older infants, iron deficiency anemia has been linked up with increased risk for stroke.[58] Thrombophilias have been identified in one-third to half of children with AIS.[29] Thrombophilias often accompany other factors influencing stroke in children.[59] Antiphospholipid (a-PL) antibodies, including lupus anticoagulant (LAC) and anti-cardiolipin (a-CL), are risk factors for neonatal stroke and prothrombotic states have been found to be associated with delayed diagnosis of ischemic stroke in newborns.[60] The prothrombin gene mutation, factor V Leiden (fVL) mutation, deficiencies in protein C, protein S, anti-thrombin III, in children, have been reported to cause ischemic stroke and bad fetomaternal outcome. Majority of thrombophilias that resulted in pediatric strokes are acquired and seldom of primary origin. Although a-CL antibodies are found in up to one-third cases of childhood stroke, apparently they do not predict risk of recurrence.[61] Lupus anticoagulants are present in patients with lupus but rarely found in healthy children. Brey et al. reported that about in 1/4th of patients with first ever stroke a-PL antibodies were present.[62] In a study by Angelini et al.,[63] 75% of children with idiopathic cerebral ischemia were positive for a-PL antibodies. We got one case of hyperhomocysteinemia in a case of homozygous A1298C gene mutation. Hyperhomocysteinemia is a potential risk factor for ischemic stroke in children as stated in their study by van Beynum et al. and Terwecoren et al.[64,65]

In regard to clinical symptoms of stroke, we have found in our study that hemiparesis (67.10%) is the commonest presenting feature with next most common being seizures (28.57%) and aphasia (25.71%), respectively, which was similar to the finding from study by Patra et al.,[16] Patil et al.,[22] and Lee et al.[18] Seizure was the most frequent presenting symptom in the Chinese study by Chung et al.[26] Signs of raised intracranial tension such as vomiting, altered consciousness, and fever were found to be significantly associated with stroke patients with infectious etiologies. Noninfectious etiologies usually presented with a focal neurological deficit (hemiparesis). While headache actually had significant association with CVT.

In our study, we used the PSOM scale for categorization and assessment of poststroke outcome. Complete recovery from neurodeficit [PSOM score 0 (zero)] was noted in 20 cases (%), whereas 40 cases (%) had persistent neurodeficit (PSOM < 5 32 cases, and PSOM > 5 8 cases). Twelve cases (17.14%) had recurrent stroke and eight cases (11.42%) died and only two (2.85%) patients were lost to follow-up. More importantly, those 40 cases who had persistent neurodeficits at follow-up at 18th month had recovered too. Regarding the outcome, in the study by Lee et al.[17] neurological deficits were shown to be present in 45% of the children; the most frequent deficit was motor impairment (24%). Another salient observation of our study was that the cases of stroke following craniocervical trauma had shown excellent recovery profile with standard management; especially, the aphasia in these cases improved splendidly within few weeks on most occasions. This is, in part, probably due to neuronal plasticity or bihemispheric representation of language. It was also seen that most of the patients with a noninfectious cause of stroke completely recovered from neurodeficit, whereas majority of the mortality were due to an infectious etiology. Noninfectious etiology thus predicted a better outcome.

The limitation of this study is a retrospective study design conducted in a single tertiary care center, and not all patients underwent uniformed evaluation, which could result in diagnostic bias. However, it is one of few reports of a relatively large Asian childhood stroke series, including a comparatively large number of moyamoya disease and MELAS patients. Second, as this is a retrospective, observational study, prevalence and incidence cannot be drawn conclusively from these data alone. These data being taken solely from a tertiary care setting cannot be projected to the general population. Some degree of recall bias is also present in our study as this being a retrospective study only, history from the caregiver cannot be relied upon completely. For further understanding the pathophysiology and improving the therapy of childhood ischemic stroke, large-scale clinical trials and continued research will be needed.

Conclusion

Ischemic stroke is fairly common in childhood compared to hemorrhagic stroke. Among AIS, vasculopathies are the commonest etiological factor. Among vasculopathies, moyamoya disease is quite common in childhood and high degree of clinical suspicion is necessary as this entity was considered rare even a decade ago. Infectious etiology of childhood stroke is an important consideration as presentation is atypical and prognosis is bad. Ischemic stroke in craniocervical trauma is common and dissection of major vessels has to be kept in mind. Proper diagnosis, early institution of treatment, and integrated approach of childhood stroke management usually fetch good outcome though outcomes depend on etiologies as well.

References

1. Goldenberg NA, Bernard TJ, Fullerton HJ, et al. Antithrombotic treatments, outcomes, and prognostic factors in acute childhood onset arterial ischaemic stroke: a multicentre, observational, cohort study. Lancet Neurol 2009;8(12):1120–1127. DOI: 10.1016/S1474-4422(09)70241-8.
2. Perkins E, Stephens J, Xiang H, et al. The cost of paediatric stroke acute care in the United States. Stroke 2009;40(8):2820–2827. DOI: 10.1161/STROKEAHA.109.548156.
3. Gardner MA, Hills NK, Sidney S, et al. The 5-year direct medical cost of neonatal and childhood stroke in a population-based cohort. Neurology 2009;74(5):372–378. DOI: 10.1212/WNL.0b013e3181cbcd48.
4. Agrawal N, Johnston SC, Wu YW, et al. Imaging data reveal a higher paediatric stroke incidence than prior US estimates. Stroke 2009;40(11):3415–3421. DOI: 10.1161/STROKEAHA.109.564633.
5. Laugesaar R, Kolk A, Uustalu U, et al. Epidemiology of childhood stroke in Estonia. Pediatr Neurol 2010;42(2):93–100. DOI: 10.1016/j.pediatrneurol.2009.08.009.
6. Mallick AA, Ganesan V, Kirkham FJ, et al. Childhood arterial ischaemic stroke incidence, presenting features, and risk factors: a prospective population-based study. Lancet Neurol 2014;13(1):35–43. DOI: 10.1016/S1474-4422(13)70290-4.
7. Kirton A, Armstrong-Wells J, Chang T, et al., The international paediatric stroke study Investigators Symptomatic neonatal arterial ischemic stroke: the international paediatric stroke study. Paediatrics 2011;128:e1402–e1410.
8. Lynch JK, Nelson KB. Epidemiology of perinatal stroke. Curr Opin Pediatr 2001;13(6):499–505. DOI: 10.1097/00008480-200112000-00002.
9. Ramaswamy V, Miller SP, Barkovich AJ, et al. Perinatal stroke in term infants with neonatal encephalopathy. Neurology 2004;62(11):2088–2091. DOI: 10.1212/01.WNL.0000129909.77753.C4.
10. deVeber GA, MacGregor D, Curtis R, et al. Neurologic outcome in survivors of childhood arterial ischemic stroke and sinovenous thrombosis. J Child Neurol 2000;15(5):316–324. DOI: 10.1177/088307380001500508.
11. Visudhiphan P, Chiemchanya S, Wattanasirichaigoon D. Strokes in Thai children: etiology and outcome. Southeast Asian J Trop Med Public Health 1996;27:801–805.
12. Kitchen L, Westmacott R, Friefeld S, et al. The pediatric stroke outcome measure: a validation and reliability study. Stroke 2012;43(6):1602–1608. DOI: 10.1161/STROKEAHA.111.639583.
13. Braun K, Kappelle L, Kirkham F, et al. Diagnostic pitfalls in paediatric ischaemic stroke. Dev Med Child Neurol 2006;48(12):985–990. DOI: 10.1017/S0012162206002167.
14. Gabis LV, Yangala R, Lenn NJ. Time lag to diagnosis of stroke in children. Pediatrics 2002;110(5):924–928. DOI: 10.1542/peds.110.5.924.
15. deVeber G, Roach ES, Riela AR, et al. Stroke in children: recognition,treatment, and future directions. Semin Pediatr Neurol 2000;7(4):309–317. DOI: 10.1053/spen.2000.20074.
16. Patra C, Sarkar S, Guha D, et al. Clinico-etiological profile of childhood stroke in a tertiary care hospital in Eastern India. J Neurosci RuralPract 2015;6(04):515–519. DOI: 10.4103/0976-3147.165414.
17. Lee YY, Lin KL, Wang HS, et al. Risk factors and outcomes of childhood ischemic stroke in Taiwan. Brain Dev 2008;30(1):14–19. DOI: 10.1016/j.braindev.2007.05.002.
18. Lee EH, Yum MS, Ko TS. Risk factors and clinical outcomes of childhood ischemic stroke in a single Korean tertiary care center. J Child Neurol 2012;27(4):485–491. DOI: 10.1177/0883073811420297.
19. Yoshida S, Yamamoto T, Yoshioka M, et al. Ischemic stroke in childhood. No Shinkei Geka 1993;21:611–616.
20. Amlie-Lefond C, Bernard TJ, Sebire G, et al. Predictors of cerebral arteriopathy in children with arterial ischemic stroke: results of the international paediatric stroke study. Circulation 2009;119(10):1417–1423. DOI: 10.1161/CIRCULATIONAHA.108.806307.
21. Rosa M, De Lucia S, Rinaldi VE, et al. Paediatric arterial ischemic stroke: acute management, recent advances and remaining issues. Ital J Pediatr 2015;41(1):95. DOI: 10.1186/s13052-015-0174-y.
22. Patil S, Adhikari-Thakke A, Gajre M, et al. Clinico-etiological profile of childhood stroke in a tertiary care hospital in Mumbai. Int J Health Sci Res 2019;9:25–30.
23. Siddiqui TS, Rehman AU, Ahmed B. Etiology of strokes and hemiplegia in children presenting at Ayub teaching hospital, Abbottabad. J Ayub Med Coll Abbottabad 2006;18:60–63.
24. Hammoodi HZ, Hammoodi LA, Al-Mahdawi A. Clinico-epidemiological study of childhood stroke in children welfare teaching hospital/Baghdad. J Faculty Med 2017;59(1):42–46. DOI: 10.32007/med.1936/jfacmedbagdad.v59i1.9.
25. Tsze DS, Valente JH. Pediatric stroke: a review. Emerg Med Int 2011;2011:734506. DOI: 10.1155/2011/734506.
26. Chung B, Wong V. Pediatric stroke among Hong Kong Chinese subjects. Pediatrics 2004;114(2):e206–e212. DOI: 10.1542/peds.114.2.e206.
27. Kirkham FJ, Prengler M, Hewes DK, et al. Risk factors for arterial ischemic stroke in children. J Child Neurol 2000;15(5):299–307. DOI: 10.1177/088307380001500506.
28. Fullerton HJ, Wu YW, Zhao S, et al. Risk of stroke in children: ethnic and gender disparities. Neurology 2003;61(2):189–194. DOI: 10.1212/01.WNL.0000078894.79866.95.
29. Ganesan V, Prengler M, McShane M, et al. Investigation of risk factors in children with arterial ischemic stroke. Ann Neurol 2003;53(2):167–173. DOI: 10.1002/ana.10423.
30. Hwang YS, Yang MS. Clinical characteristics of childhood cerebrovascular disease and analysis on the prognostic factors. J Korean Pediatr Soc 1995;38:353–365.
31. Golomb MR, Fullerton HJ, Nowak-Gottl U, et al. Male predominance in childhood ischemic stroke: findings from the international pediatric stroke study. Stroke 2009;40(1):52–57. DOI: 10.1161/STROKEAHA.108.521203.
32. Mackay MT, Wiznitzer M, Benedict SL, et al. Arterial ischemic stroke risk factors: the international pediatric stroke study. Ann Neurol 2011;69(1):130–140. DOI: 10.1002/ana.22224.
33. Scott RM, Smith ER. Moyamoya disease and moyamoya syndrome. N Engl J Med 2009;360(12):1226–1237. DOI: 10.1056/NEJMra0804622.
34. Kim SK, Cho BK, Phi JH, et al. Pediatric moyamoya disease: an analysis of 410 consecutive cases. Ann Neurol 2010;68(1):92–101. DOI: 10.1002/ana.21981.
35. Kim SK, Seol HJ, Cho BK, et al. Moyamoya disease among young patients: its aggressive clinical course and the role of active surgical treatment. Neurosurgery 2004;54(4):840–844. DOI: 10.1227/01.NEU.0000114140.41509.14.
36. Chabrier S, Husson B, Lasjaunias P, et al. Stroke in childhood: outcome and recurrence risk by mechanism in 59 patients. J Child Neurol 2000;15(5):290–294. DOI: 10.1177/088307380001500504.
37. DeVeber G, The Canadian Pediatric Ischemic Stroke Study Group Canadian paediatric ischemic stroke registry: analysis of children with arterial ischemic stroke. Ann Neurol 2000;48:514.
38. Testai F, Gorelick P. Inherited metabolic disorders and stroke part 1: fabry disease and mitochondrial myopathy, encephalopathy, lactic

acidosis, and strokelike episodes. Arch Neurol 2010;67(1):19–24. DOI: 10.1001/archneurol.2009.309.
39. Testai F, Gorelick P. Inherited metabolic disorders and stroke part 2: homocystinuria, organic acidurias, and urea cycle disorders. Arch Neurol 2010;67(2):148–153. DOI: 10.1001/archneurol.2009.333.
40. Koga Y, Povalko N, Nishioka J, et al. MELAS and l-arginine therapy: pathophysiology of stroke-like episodes. Ann N Y Acad Sci 2010;1201(1):104–110. DOI: 10.1111/j.1749-6632.2010.05624.x.
41. Sträter R, Becker S, von Eckardstein A, et al. Prospective assessment of risk factors for recurrent stroke during childhood-a 5-year follow-up study. Lancet 2002;360(9345):1540–1545. DOI: 10.1016/S0140-6736(02)11520-0.
42. Younkin DP. Diagnosis and treatment of ischemic pediatric stroke. Curr Neurol Neurosci Rep 2002;2(1):18–24. DOI: 10.1007/s11910-002-0048-8.
43. Rivers RP, Hathaway WE, Weston WL. The endotoxin-induced coagulant activity of human monocytes. Br J Haematol 1975;30(3):311–316. DOI: 10.1111/j.1365-2141.1975.tb00547.x.
44. Esmon CT, Taylor Jr FB, Snow TR. Inflammation and coagulation: linked processes potentially regulated through a common pathway mediated by protein C. Thromb Haemost 1991;66(01):160–165. DOI: 10.1055/s-0038-1646385.
45. Woodhouse PR, Khaw KT, Plummer M, et al. Seasonal variations of plasma fibrinogen and factor VII activity in the elderly: Winter infections and death from cardiovascular disease. Lancet 1994;343(8895):435–439. DOI: 10.1016/S0140-6736(94)92689-1.
46. Ameriso SF, Wong VL, Quismorio Jr FP, et al. Immunohematologic characteristics of infection-associated cerebral infarction. Stroke 1991;22(8):1004–1009. DOI: 10.1161/01.STR.22.8.1004.
47. Askalan R, Laughlin S, Mayank S, et al. Chickenpox and stroke in childhood: a study of frequency and causation. Stroke 2001;32(6):1257–1262. DOI: 10.1161/01.STR.32.6.1257.
48. Sebire G, Meyer L, Chabrier S. Varicella as a risk factor for cerebral infarction in childhood: a case- control study. Ann Neurol 1999;45(5):679–680. DOI: 10.1002/1531-8249(199905)45:5<679::AID-ANA22>3.0.CO;2-E.
49. Fullerton HJ, Johnston SC, Smith WS. Arterial dissection and stroke in children. Neurology 2001;57(7):1155–1160. DOI: 10.1212/WNL.57.7.1155.
50. Tan MA, Armstrong D, MacGregor DL, et al. Late complications of vertebral artery dissection in children: pseudoaneurysm, thrombosis, and recurrent stroke. J Child Neurol 2009;24(3):354–360. DOI: 10.1177/0883073808324775.
51. Fusco MR, Harrigan MR. Cerebrovascular dissections--a review part I: spontaneous dissections. Neurosurgery 2011;68(1):242–257. DOI: 10.1227/NEU.0b013e3182012323.
52. Ganesan V, Cox TC, Gunny R. Abnormalities of cervical arteries in children with arterial ischemic stroke. Neurology 2011;76(2):166–171. DOI: 10.1212/WNL.0b013e318205d4d5.
53. Tan MA, DeVeber G, Kirton A, et al. Low detection rate of craniocervical arterial dissection in children using time-of-flight magnetic resonance angiography: causes and strategies to improve diagnosis. J Child Neurol 2009;24(10):1250–1257. DOI: 10.1177/0883073809333539.
54. Rafay MF, Armstrong D, DeVeber G, et al. Craniocervical arterial dissection in children: clinical and radiographic presentation and outcome. J Child Neurol 2006;21(1):8–16. DOI: 10.1177/08830738060210010101.
55. Dlamini N, Freeman JL, Mackay MT, et al. Intracranial dissection mimicking transient cerebral arteriopathy in childhood arterial ischemic stroke. J Child Neurol 2011;26(9):1203–1206. DOI: 10.1177/0883073811408904.
56. Blau EB, Morris RF, Yunis EJ. Polyarteritis nodosa in older children. Pediatrics 1977;60:227–234.
57. Lanthier S, Lortie A, Michaud J, et al. Isolated angiitis of the CNS in children. Neurology 2001;56(7):837–842. DOI: 10.1212/WNL.56.7.837.
58. Hartfield DS, Lowry NJ, Keene DL, et al. Iron deficiency: a cause of stroke in infants and children. Pediatr Neurol 1997;16(1):50–53. DOI: 10.1016/S0887-8994(96)00290-1.
59. Chan AK, deVeber G. Prothrombotic disorders and ischemic stroke in children. Semin Pediatr Neurol 2000;7(4):301–308. DOI: 10.1053/spen.2000.20075.
60. Golomb MR, MacGregor DL, Domi T, et al. Presumed preor perinatal arterial ischemic stroke: risk factors and outcomes. Ann Neurol 2001. 50163–50168.
61. Lanthier S, Lindsay S, Mitchel L, et al. Anticardiolipin antibodies are associated with cardioembolic stroke but do not predict recurrent cerebral ischemia in children. Neurology 2003;56:A11–A11.
62. Brey RL, Hart RG, Sherman DG, et al. Antiphospholipid antibodies and cerebral ischemia in young people. Neurology 1990;40(8):1190–1196. DOI: 10.1212/WNL.40.8.1190.
63. Angelini L, Ravelli A, Caporali R, et al. High prevalence of antiphospholipid antibodies in children with idiopathic cerebral ischemia. Pediatrics 1994;94:500–503.
64. van Beynum IM, Smeitink JA, den Heijer M, et al. Hyperhomocysteinemia: a risk factor for ischemic stroke in children. Circulation 1999;99(16):2070–2072. DOI: 10.1161/01.CIR.99.16.2070.
65. Terwecoren A, Steen E, Benoit D, et al. Ischemic stroke and hyperhomocysteinemia: truth or myth? Acta Neurol Belg 2009;109(3):181–188.