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Case Report

Risk factors and outcomes, a case series of ischemic stroke in children

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Ischemic strokes in children, although generally rare events, are more prevalent than commonly believed. Ischemic stroke in children have been associated with coagulation disorders, cardiac anomalies, infections and trauma.

Cerebrovascular disorders are among the top 10 causes of death in children.[1] Stroke in children, 55% is believed to be ischemic and the remainder is hemorrhagic.[2] Ischemic stroke is defined as cerebrovascular disorders caused by sudden occlusion of cerebral arteries or veins resulting in focal cerebral damage and clinical neurologic deficit lasting more than 24 hours. Ischemic stroke in children are reported to have a prevalence of 0.63 to 7.9 per 100,000 children.[3,4,5] In these children, multiple risk factors are often identified in a single child and in the remaining 50% - so called cryptogenic stroke with no clear risk factors at presentation.[6]

In every child with stroke underlying predisposing condition or conditions should be sought and treatment of risk factors is essential because children may remain at risk for recurrent strokes and adverse outcomes are linked to the type and number of risk factors. We present three children with two or more of these risk factors, indicating multi factorial causes of strokes in children. Prognosis after stroke is difficult to predict.

The cases

Three patients who had been diagnosed with stroke were evaluated at our institution between March 2004 and November 2007, with characteristics as displayed in **Table 1**. All patients were girls (ages 1-3 years). They were evaluated by pediatric neurology, hematology and cardiology consultants. Evaluations included neuro-imaging (computed tomography/CT, magnetic resonance imaging/MRI, magnetic resonance angiography), coagulation studies and echocardiography.

Case 1

A one-year and two-month old female infant was admitted in March 2004. One day prior to admission, she was seen to fall 30 cm from a stair onto a floor, bumped her head at the bottom but appeared uninjured, with no impairment of consciousness. By the next morning, she was noted to lost her balance

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Table 1. Ischemic Stroke in Children: Clinical Findings

Case	Age	Sex	Presentation	Neurologic abnormalities	Coagulopathy	Associated Factors
1	1 2/12	F	weakness of L leg and arm; deviation of mouth to the R side	L Hemiparesis; L UMN facial nerve palsy	↓ protein C ↓ protein S	Trauma Anemia Thrombocytosis
2	1 11/12	F	weakness of right arm and both legs	Tetraparesis	↓ protein C	Trauma
3	3	F	dragging L foot; drooling out of the L side of mouth	L Hemiparesis; L UMN facial nerve palsy	↓ protein C	Anemia Thrombocytosis

Table 2. Coagulation Studies

Coagulation Factors	1	2	3
Protein C (%)	90 (113)	63 (115)	74 (88)
Protein S (%)	49 (89)	83 (88)	105 (92)
Antithrombin III (%)	112 (89)	ND	ND
Anticardiolipin IgG/IgM	negative/negative	ND	ND

( ) Normal value, ND : not determine

when she sat and developed weakness of her left arm, leg as well as left facial weakness**.** Physical examination showed left upper motor neuron facial nerve palsy and left hemiparesis. Complete blood count showed microcytic hypochromic anemia and thrombocytosis. Her coagulation tests and echocardiography were normal (**Table 2**). Cranial CT scan suggested infarct in right basal ganglia (**Figure1**).

Our impression was ischemic stroke, suggested of iron deficiency anemia and moderate wasting. Aspirin at 3.75 mg/kg/day was initiated and she was discharged with improvement of her left leg. She had regular follow up and after several physiotherapy sessions, she was able to walk alone for around five steps.

One month later, she developed sudden weakness on her left arm and leg. She was extensively investigated for recurrent stroke. Investigations showed protein C and S deficiency. D-dimer, anticardiolipin and anti thrombin III were normal (**Table 2**) Repeated cranial CT scan showed multiple infarct involving right basal ganglia and right parieto-occipital (**Figure 2**). MRI showed infarct in the right lateral caudate nucleus. (**Figure 3**).

The impression was recurrent ischemic stroke due to protein C and S deficiency. Aspirin at the same dose was given and warfarin at 0.2 mg/kg was initiated. Subsequent follow up after three years, her hand was still fisted but she was able to open her left hand slowly, with gait disturbances. Hemineglect sinistra was noted.

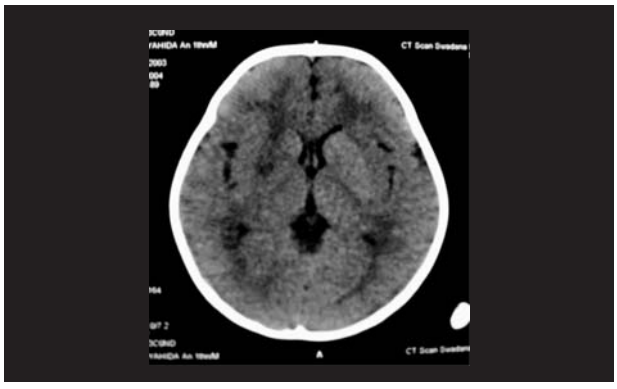

Figure 1. Infarct in right basal ganglia

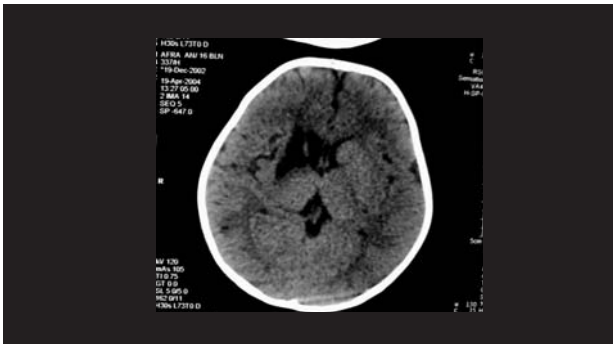

Figure 2. Multiple infarct involving right basal ganglia and right parietooccipital

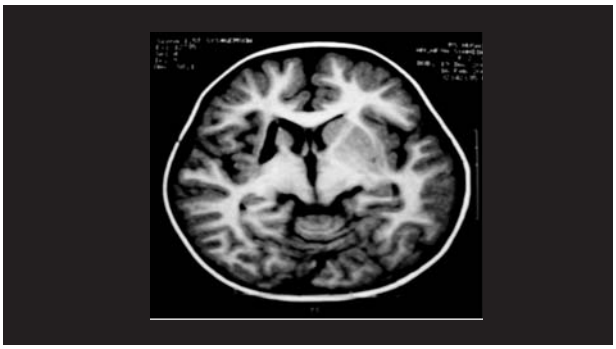

Figure 3. Infarct in the right lateral caudate nucleus

Case 2

A one-year and 11-month old girl was admitted in December 2006 due to weakness of right arm and both legs since two weeks prior to admission. One month prior to admission, she had a fall 50 cm from a chair and cried immediately. Examination suggested tetraparesis. Cranial CT scan showed hypodensity lesion involving frontal, temporal, parietal, bilateral lobe and bilateral centrum semiovale (**Figure 4**).

Coagulation studies showed protein C deficiency (**Table 2**). Her impression was ischemic stroke due to protein C deficiency. Warfarin at 0.04 mg/kg was given. After four days of warfarin, improvement of her movement was noted. She made a complete clinical recovery within three months of the initial event.

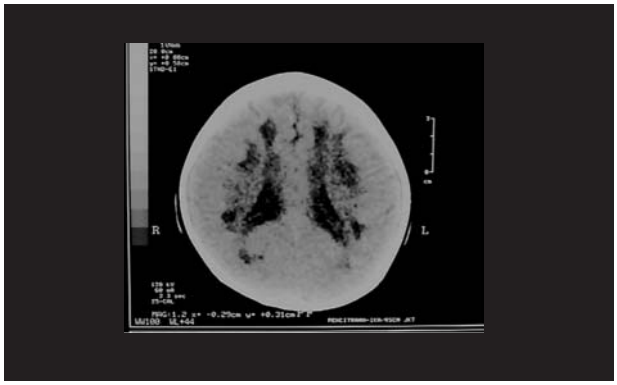

Figure 4. Hypodens lesion involving frontal, temporal, parietal bilateral lobe and semiovale centrum bilateral

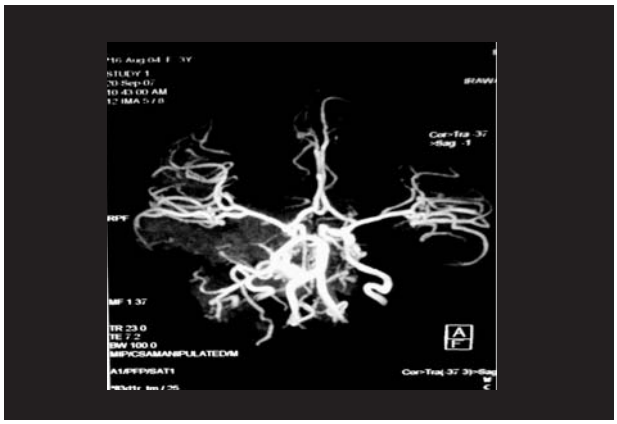

Figure 5. Hyperacute ischemic lesion on right globus pallidus and anomaly of left posterior cerebral artery

Case 3

A three-year old girl was admitted in September 2007 with chief complaint of dragging her left foot since three days prior to admission. She developed left sided weakness involving her left arm and leg. She began drooling out of the left side of her mouth. There was no history of fall. She had a brother who died at the age of 22 months old due to fever, hematemesis and bluish spots on his body. Examination revealed left central facial palsy and left hemiparesis. Blood examination showed microcytic hypochromic anemia, thrombocytosis and protein C deficiency (**Table 2**). Consultation was done to hematologist, warfarin at 0.2 mg/kg was given. Cranial CT scan showed normal result. She was discharged with improvement of her hemiparesis. MRA done after nine days showed hyperacute ischemic lesion on right globus pallidus and anomaly of left posterior cerebral artery (**Figure 5**.) She made a gradual improvement and a month later was neurologically normal.

Discussion

Weakness of sudden onset in a child causes much alarms, it may be due to central nervous system (CNS) and peripheral nervous system (PNS) lesions. The differential diagnoses lie on the history and the neurologic examination findings. The distribution and pattern of weakness are greatly dependent on the site of pathology. For example, CNS lesions affecting one hemisphere produce a contralateral hemiparesis with upper motor neuron signs. Initially, the muscle tone may be flaccid but shortly thereafter it is replaced by spasticity. There is also a differential weaknesses, brisk deep tendon reflexes (DTRs) and pathological reflexes such as Babinski. On the other hand, lesions affecting the PNS produce a flaccid type of weakness, which is greatly dependent upon the site of pathology, hypoactive to absent DTRs and absence of pathological reflexes.[7]

Brain damage resulting from stroke occurs in one of two general forms such as ischemia and hemorrhage. Ischemic injury of brain occurs as a result of one of three mechanisms: embolism, thrombosis, or diminished systemic perfusion.[8] Embolic stroke presents with an abrupt (apoleptic) onset, whereas

thrombotic strokes present with a subacute or staggering course. At times these two overlap and may be difficult to distinguish one from the other.[7]

Stroke occurs rarely in children, and the recognition often delayed beyond 24 hours. The total time delay was longer for ischemic stroke than the hemorrhage**:** 42.8 hours (median: 20 hours; range 0.1 - 300 hours) for ischemic stroke and 14.3 hours (median: 5 hours; range 0.1 – 60 hours) for hemorrhage.[9] Ischemic stroke typically presents with focal neurologic deficits, like hemiparesis (94%), followed by fever/prodrome (35%-40%), change in mental status (28%), headache (22%), and seizure (16%).[10] We found hemiparesis in two of our patients and tetraparesis in one patient. Cardiac disease is the most common cause of stroke in childhood[6] frequently in children less than two years old.[11] In our cases, none of them have signs and symptoms suggestive cardiac disease. At least one third of childhood stroke occurs in association with infection.[6] The prevalence of arterial ischemic stroke in children with bacterial meningitis has been reported as high as 27%[3] and varicella has been estimated at one per 15,000 children.[12,13] Neither fever nor history of varicella were found in our patients.

Prothrombotic disorders are abnormalities of the coagulation system, fibrinolytic system, endothelial cells, or platelets. Inherited or acquired coagulation system disorders have been identified in 20% to 50% of children presenting with arterial ischemic stroke. There was various prothombotic risk factors, including protein C and S deficiency.[14,15] In case 1, we found protein C, S deficiency and thrombocytosis, in case 2 and III there was only protein C deficiency. Protein C and S deficiency can be inherited or acquired.[2,16] No definite etiology were found in our patients. In case 3, inherited protein C deficiency might be considered.

Anemia is noted in more than 25% of children with stroke. Two of our cases had anemia. Iron deficiency anemia has been implicated in stroke and is an important stroke risk factor because it is easily treatable.[6,14] Cervicocephalic arterial dissection may be spontaneous or traumatic with male predominance. The cervical or vertebral vessels are typically affected. Initial symptoms may be nonspecific.[10,17] Four-vessel conventional angiography remains the gold standard.[2] Cerebral vasculitis is an uncommon cause of stroke in children. Schoenberg *et al* did not find any cause of vasculitis in children younger than 14 years of age.[4]

Central nervous system vasculitis in childhood may be primary angiitis of CNS or secondary to a variety conditions including infections, collagen vascular diseases and malignancies. Because of the lack of typical or pathognomonic features, diagnosis is difficult. Angiitis is suspected when neurological signs an symptoms remain unexplained or when the angiographic appearance is consistent with arteritis.[18]

Moyamoya disease (MMD) is a nonatherosclerotic, noninflammatory, vasculopathy characterized by chronic progressive stenosis or occlusion of the large cerebral arteries. In angiogram, there is "puff of smoke", commonly presenting during the first decades of life. Presenting symptoms of MMD include headache, progressive cognitive decline, seizures, and strokes.[14]

There was history of trauma in 1st and 2nd patient. Cerebral infarction is an exceedingly rare sequel. It should only be made after systematic exclusion of other causes. The pathophysiology of stroke after mild head injury in young children is either thrombus or spasm of lenticulostriate branches of middle cerebral artery. These vessels are end arteries. In case 1 , there was history of trauma and infarct in the basal ganglia (caudate nucleus) that are supplied by lenticulostriate branches of middle cerebral artery.[19,20]

A guideline by the UK Royal College of Physicians pediatric stroke working group (2004) has been published. The guidelines dealing mainly with the diagnosis, investigation and management of acute arterial ischemic stroke in children beyond the neonatal period, covering acute presentation, management and longer term care. They emphasize the need for early imaging and input from a pediatric neurology tertiary centre. They also appropriately emphasize that these children should be investigated for an underlying prothrombotic tendency and should undergo echocardiography.[21]

Timing of studying coagulation parameters is an issue. It is cost effective to avoid testing for protein C and S and antithrombin III activity levels at initial presentation as levels may be reduced with acute thrombosis. Ideally, testing for these plasma proteins should occur at least two weeks post-thrombosis. However, if tests are done in the acute phase and plasma levels are in the normal range, then protein C

and S, and antithrombin III deficiencies are essentially excluded.[22]

The goal of stroke treatment is to limit infarct size, improve outcome, and prevent recurrence.[10] The working group found no studies specially examining on the efficacy of acute treatments and recommend it based on consensus opinion. It could be suggested that whether or not to the give a child with cardiac embolism, an anti-coagulate, the decision should be made based on the individual patient. By contrast, good evidence exists for the use of 5 mg/kg body weight aspirin per day unless imaging results suggesting an intracranial hemorrhage or the child has sickle cell disease.[21]

Stroke recurrence is a major concern for children and their families. Arterial ischemic stroke recurs in about 6 to 30%, with its increased in children with multiple risk factors such as in those with protein C deficiency, increased levels of lipoprotein, vascular diseases.[23] Guidelines for secondary prevention in children is anticoagulation, and it should be considered if there is recurrence of stroke despite treatment with aspirin,[21] we did exactly the same with our first patient who received warfarin when she had recurrence stroke. Forty-five percent children with stroke had permanent neurologic deficit.[23] The most frequently reported neurologic impairment is hemiparesis.[21]

Factors predicting poor outcome in childhood arterial ischemic stroke include age younger than 12 months, presentation with an altered level of consciousness or seizures, infarcts occupying more than 10% of intracranial volume, presence of bilateral infarction or of infarction involving both the internal capsule and the cortical middle cerebral artery territory and need for rehabilitation therapy after stroke.[24,25] In a recent retrospective review, if a patients found to have multiple risk factors for stroke, the recurrence risk was 42%, while only 8% of patients with a single risk factor recurred.[23] In case 1, the patient had multiple risk factors such as protein C and S deficiency, anemia, thrombocytosis and history of trauma with factor predicting poor outcome include multiple infarcts and therefore need for rehabilitation therapy after stroke.

The case fatality rate for arterial ischemic stroke is reported to be as high as 21%.[23] The mortality rate is due to stroke in children aged 1 to 15 years was 0.6 per 100,000 children in United States in 2001.[3] Stroke in childhood is not only a terrifying event at the time of acute episode, but remains a significant burden on long-term follow-up. Careful primary care and follow-up are mandatory. Our small series of cerebrovascular events in childhood emphasizes the importance of this multidisciplinary approach to this disorder, which can lead to appropriate therapy that should reduce future morbidity.

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