Epidemiology and Outcomes of Arterial Ischemic Stroke in Children Admitted to Tabriz Children's Hospital, Tabriz, Iran during (2014-2019)

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Abstract

Background

Arterial ischemic stroke (AIS) is an important cause of neurological disabilities, such as hemiparesis, epilepsy, and cognitive dysfunction in children. This study aimed to describe the clinical presentation, risk factors, and neuroimages of pediatric patients with AIS.

Materials and Methods: In a cross sectional study all of 73 patients admitted to Tabriz children's hospital with the diagnosis of Ischemic stroke between 2014 and 2019 were enrolled in the study and follow up for at least one year after discharge. Stroke was diagnosed based on clinical presentation and compatible Brain CT scan and MRI, or MRV/MRA and then Para clinical assessment were done.

Results: Male predominance in the present have been observed with male/female ratio of 1.28. AIS was common in younger age (79.4% <2 years n=58). Children younger than 1 year significantly had had seizures (61.8%) (P<0.01) and altered mental status (67.9%) (P<0.01), while and children older than one year had shown focal weakness (62.3%) (P<0.01). The most frequent risk factors included acute illness and (34.2%), cardiac disorders (23.3%). There was no hospital mortality in our study. 60.3% of the children had demonstrated neurological deficits. Outcome in children less than one year was better than older children (P<0.01) There were no difference between male and female in outcome of the stroke (P>0.05).

Conclusion

With careful investigation, in most of the children underlying risk factors could be found. Based on the results, acute illness and cardiac disorders were the most frequent risk factors in pediatric stroke. However, some of these risk factors (such as anemia, infection, and dehydration) which are relatively common in the pediatric population were preventable.

Key Words: Arterial Ischemic Stroke, Pediatric, Risk Factors, Outcome.

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1- INTRODUCTION

In children, arterial ischemic stroke (AIS) is one of the main reasons for neurological disabilities, such as hemiparesis, epilepsy, and cognitive dysfunction (1, 2) Childhood stroke is referred to those strokes occurring between the age of 1 month and 18 years (3). The incidence rate of childhood stroke has been reported between 2 and 13/100,000 children/year (4) with a mortality rate of about 5% (5). Population-based studies have also shown that the incidence of stroke among Asian children is likely to be within the range of 1.9 to 2.1 per 100,000 children per year (6). For example, an Iranian study reported an incidence of 1.8 per 100,000 children per year (7). Also, over half of the stroke have been reported in children less than 36 months (6). It has been further announced that at least two thirds of survivors are likely to suffer from long-term sequels such as developmental and behavioral disabilities or epilepsy (5).

A large group of children with AIS have been also diagnosed with other medical conditions, such as sickle cell disease, congenital heart disease, acute systemic diseases or a range of genetic disorders, which predispose children to stroke (8). In adulthood, atherosclerosis is the predominant cause of stroke, while in childhood, cause of stroke could markedly differ. Common risk factors for childhood stroke can be categorized in three groups of arteriopathy, cardiac disease, and prothrombotic disorders. Other risk factors include infection, sickle cell disease, trauma, and genetic or metabolic disorders (1, 9). Most perinatal strokes are characterized by focal seizures, which are predominantly observed in older children as well. Some infants exhibit no symptoms in the perinatal period. Such patients' conditions are not detected until a hemiparesis is noted later. In addition, childhood stroke typically display acute focal neurological deficits such as hemiparesis (9). The aim of this study was to describe the clinical presentation, risk factors, and neuroimages of pediatric patients with AIS.

2- MATERIALS AND METHODS

2-1. Study design and population

In a cross sectional study all of patients admitted to Tabriz children's hospital, Tabriz, Iran, with the diagnosis of Ischemic stroke between 2014 and 2019 were enrolled in the study and follow up for at least one year after discharge. All of 73 stroke patients who were admitted to Tabriz children's hospital from 2014 to 2019 were analyzed. Stroke was diagnosed based on clinical presentation and compatible Brain CT scan and MRI, or MRV/MRA and then Para clinical assessment were done. The lab test included CBC diff, CRP, ESR, electrolytes, lipid profile, anti-thrombin C and S, Factor V Leiden, lactate, Ammonia, homocysteine level, Lupus anticoagulant, Anticardiolipin antibodies, Fe, TIBC, PT,PTT and LP (if needed). Cardiologic insult were done for all patients. The risk factors were included in different categories: arteriopathy, infection, prothrombotic states, cardiac disorders, acute systemic conditions, head and neck trauma. During follow up the patients were assessed as seizure and focal neurologic sequels.

2-2. Inclusion and exclusion criteria

Inclusion criteria were the age 1 month to 16 years with stroke who were admitted to children's hospital in Tabriz, Iran. We excluded neonatal stroke patients due to different etiologies, presentations, and outcomes.

2-3. Ethical consideration

This study closely followed Helsinki instructions and guidelines for medical research on children.

The Organizational Committee of Research Ethics, Tabriz University of medical sciences, approved the study protocol (permit number: IR.TBZMED.REC.1398.731). The patients' confidentiality was assured through the end of the study.

2-4. Data Analysis

All the collected data were analyzed using SPSS software version 20.0. Descriptive statistics (frequency, percentage, mean ± standard deviation) were used for statistical analysis. Also, Chi-square and Fisher's exact tests were used to compare the qualitative findings. P-value less than 0.05 were statistically significant.

3- RESULTS

3-1. Patient Characteristics

Over the 5-year study period (2014-2019), 73 patients (aged between 1 month and 16 years), had been admitted to Tabriz children's hospital with acute stroke. The children' mean age was 28.52±35.9 months. Moreover, there were 32 (43.8%), and 41 (56.2%) females males, respectively. At the onset of the stroke, more than half of the patients (79.4%) were younger than two years, whereas nearly half of them (45.2%) were younger than one years. The median age at stroke presentation was also 15 months.

3-2. Presentation

The studied children had frequently shown focal neurological deficits (83.6%) or seizures (46.6%). Symptoms observed in patients are summarized in **Table.1.** Children younger than one year significantly had had seizures and altered mental status; while and children older than one year had shown focal weakness (**Table.2**).

Table-1: presentation sign/symptoms in children with arterial ischemic stroke, n=73

Sign/symptoms	Number (%)
focal neurological deficits	61 (83.6%)
Seizures	34 (46.6%)
Altered Sensorium	28 (38.3%)
Hemifacial Weakness	16 (21.9%)
Restless	8 (11%)
Fever	18 (24.7%)
Ataxia	5 (6.8%)
Headache	3 (4.1%)
Vomiting	3 (4.1%)
Dysarthria	3 (4.1%)
Aphasia	6 (8.2%)

Table-2: Frequency of symptoms in children with arterial ischemic stroke by age groups.

Presenting sign/symptoms	< 1 year (n=33)	>1 year (n=40)	P-value
Focal Neurological Deficits	23 (37.7%)	38 (62.3%)	0.004
Seizures	21 (61.8%)	13 (38.2%)	0.008
Altered Sensorium	19 (67.9%)	9 (32.1%)	0.002

3-3. Diagnosis

Stroke diagnosis was confirmed by either CT (in 71% of patients) MRI, or angiography CT. According to **Table.3**, the most commonly involved artery in children with acute stroke is the middle cerebral artery (MCA) (78%). This table also shows that Infarcts were observed in multiple brain structure categories in 5.4%, and in bilateral lesions in 8.2% of our sample. There were also two patients with CVST all of whom were above 6 years of age.

Table-3: Affected vascular territory in children with arterial ischemic stroke, n=73.

Vascular territory	Number of cases (%)
Anterior circulation territory	51 (69.8%)
Basal ganglia involvement	12 (16.4%)
Posterior circulation territory	12 (16.4%)
Thalamus involvement	3 (4.1%)
Bilateral	6 (8.2%)
Multiple (anterior and posterior) arteries	4 (5.4%)

3-4. Risk factors

All the studied patients except one (1.4%) children had at least one risk Factor. Risk factors are summarized in **Table.4**.

Table-4: Risk factors of arterial ischemic stroke in children, n=73.

Etiology	Number/Percentage	Subgroups: Number/Percentage
Cardio embolic	17 (23.3%)	Arrhythmia 4(23.5%) Open heart surgery 4(23.5%) Cyanotic heart disorder 7(41.2%) Myocarditis 1(5.9%) PFO 1(5.9%)
Acute illness	25 (34.2%)	Sepsis 7(28%) Meningitis 4(16%) Encephalitis 4(16%) Sinusitis and periorbital infection 3(12%). Dehydration 4 (16%) Opiate poisoning 3 (12%)
Vascular disorder	8 (11%)	Arteriopathies 4(50%) Postvaricella angiopathy 2(25%) AVM 1(12.5%) Moyamoya disease 1(12.5%)
Prothrombotic condition	5 (6.9%)	Factor V Leiden 1(20%), Antiphospholipid antibody 1(20%) Anemia 3(60%)
Trauma	14 (19.2%)	
MELAS	1 (1.4%)	
Unknown	1 (1.4%)	

MELAS: Mitochondrial Encephalopathy, Lactic acidosis, and Stroke-like episodes, PFO: Patent foramen ovale, AVM: Arteriovenous malformation.

3-5. Treatment

Antithrombotic therapy and anticoagulant agents had been provided to all children. Based on need, they had also received long-time (18-24 months) aspirin (5 mg/kg/ day) treatment.

3-6. Outcome

There was no hospital mortality in our study. Although 29 children, who survived stroke, had been in a good outcome, with no neurological sequel, 60.3% of the children had demonstrated neurological deficits (**Table.5**), most commonly hemiparesis and seizure (21/44, 47.7%), during follow-up. Children more than one year had tendency to have more neurologic deficits. There were no difference between male and female in neurological deficits and outcome of the stroke (**Table.6**). Besides, most children had demonstrated a reduction in their deficit severity during one-year follow up, while 6.8% of them had remained stable.

Table-5: Outcome in children with arterial ischemic n=73.

Outcome	Number (%)	Mild	Moderate to Severe
Without neurological deficits	29 (39.7%)	-	-
With neurological deficits	44 (60.3%)	33 (75%)	11 (25%)

Table-6: Outcome in children with arterial ischemic stroke by age and gender groups.

Outcome	< 1 year (n=33)	>1 year (n=40)	Male (n=41)	Female (n=32)
Without neurological deficits	19 (65.5%)	10 (34.5%)	23 (59%)	16 (41%)
With neurological deficits	14 (31.8%)	30 (68.2%)	18 (52.9%)	16 (47.1%)
P value	P=0.005		P>0.05	

3-7. Recurrence

Following the initial stroke event, 8 0f 73 patients (11%) had experienced recurrent AIS. Also, the rate of Transient ischemic attack (TIA) before the AIS had been 8.2%. Children more than one year had tendency to TIA (P>0.05) (**Table.7**).

Table-7: TIA in children with arterial ischemic stroke by age groups.

TIA	< 1 year (n=33)	>1 year (n=40)
Without TIA	31 (46.3%)	36 (53.7%)
With TIA	2 (33.3%)	4 (66.7%)
P-value	P>0.05	

TIA: Transient ischemic attack.

4- DISCUSSION

The present study aimed to describe the clinical presentation, risk factors, and neuroimages of pediatric patients with AIS. According to the findings of the present study, male predominance in the present have been observed with male/female ratio of 1.28. AIS was common in younger age (79.4% <2 years). Children younger than 1 year significantly had had seizures (61.8%) (P<0.01) and altered mental status (67.9%) (P<0.01),

while and children older than one year had shown focal weakness (62.3%) (P<0.01). The most commonly involved artery in children with acute stroke is the middle cerebral artery (MCA) (78%). Stroke in anterior circulation territory was more common than posterior circulation territory. The most frequent risk factors included acute illness and (34.2%), cardiac disorders (23.3%). There was no hospital mortality in our study. 60.3% of the children had demonstrated neurological deficits. Outcome in children less than one year was better than older children (P<0.01) There were no difference between male and female in outcome of the stroke. There was no statistically significant difference between male and female in stroke outcome. Following the initial stroke event, 8 0f 73 patients (11%) had experienced recurrent AIS. Also, the rate of TIA before the AIS had been 8.2%. The present study was in line with some studies in which gender and ethnic disparities have been noted. Studies have shown that pediatric stroke may be more common in boys than in girls (10).

In present study, seizure and focal weakness dominancy was noticed in children younger than one year and those who were older than one year, respectively. Childhood AIS seems to be more frequent in children, who are less than 1 year old (2). Stroke children, who are younger than one year usually have epileptic seizures, irritability, and altered mental status compared to those who are older than one year who show focal weakness, usually hemiparesis (6, 11). In the current study, moreover, the most commonly involved artery was found to be the MCA that confirmed reports in the literature. Involvement of the ACA has been mostly seen in combination with an MCA lesion (12). In this study, most of the children had at least one risk Factor. The most frequent risk factors were acute illness (included infection) and cardiac

disorders. In the International Pediatric Stroke Study (IPSS), 9% of the children had no identifiable risk factor. In other studies, the most common risk factors have been reported to be arteriopathies (53%), cardiac disorders (31%), and infection (24%) (13, 14). Furthermore, in the present work, 23.3% of children had been diagnosed with an obvious cardiac condition, including arrhythmia (23.5%), open-heart surgery (23.5%), cyanotic heart disorder (41.2%), myocarditis (5.9%), and patent foramen ovale (PFO) (5.9%). In another international registry of children with AIS, nearly one-third of the patients had cardiac disease as the primary underlying etiology (15). Cardiac diseases, such as congenital malformations, cardiomyopathies, endocarditis, and arrhythmias and especially children with cyanotic CHD are common predisposing factors for pediatric stroke including (15, 16).

Any catheterization and potential right-to-left shunt exacerbate the risk (16). One-quarter of arterial ischemic strokes in children with cardiac disease occur in the peri-procedural period (17) Children with particular cardiac lesions, such as single ventricle physiology and cardiomyopathy appear to be at greater risk. (18) Compared to children without cardiac disease, those who do not suffer from cardiac disease tend to have multiple bilateral strokes involving both the anterior and posterior circulations (18). In the current study, there was one patient with PFO. Although studies on young adults have suggested a role for isolated PFO as a risk factor for stroke, further research is required in children (18). In this study, we also perceived that the most common definable vascular disorders had been arteriopathies (62.5%), postvaricella angiopathy (12.5%), arteriovenous malformation (AVM) (12.5%), and moyamoya disease (12.5%). Arteriopathy refers to disorders of cerebral arteries that predispose patients to stroke.

It also accounts for over 50% of AIS in older children. Arteriopathy include arterial dissection, Moyamoya, and inflammatory condition. On the other side, a monophasic, self-limited form termed transient cerebral arteriopathy of childhood (TCA) is a common cause of AIS in children. The underlying pathophysiology of TCA is thought to be partially mediated by a post infectious inflammatory process. One of the strong association with TCA is Varicella infections. When TCS occurs at the ages less than 12 months after chicken pox, it is called post-varicella angiopathy. Other associated infections observed in a smaller number of patients include unspecified upper respiratory infections, EpsteinBarr virus, herpes simplex virus 1, and enterovirus (16, 19).

Moreover, prothrombotic disorders, both congenital and acquired, have been proven to be associated with 20-50% of strokes in children. Other hematological disturbances associated with pediatric stroke are iron-deficiency anemia and polycythemia (16). In older children, metabolic disorders may also produce stroke or stroke-like episodes, including MELAS, Fabry disease, and hyperhomocysteinemia (16). Physiological features, such as slower blood flow and coagulation system are particularly important in CSVT pathophysiology. In addition, venous congestion could lead to focal cerebral edema, which could in turn progress into venous infarction and hemorrhage. The most common risk factors for CSVT are dehydration and prothrombotic disorders (16).

There was no hospital mortality in our study but 60.3% of the children had demonstrated neurological deficits. Generally, children survive stroke more than adults. However, children have significant long-term neurological, cognitive and behavioral disorders. Tham et.al showed that up to 75% of survivors had residual neurological deficits 5 years after stroke (20). It has been also verified that infants could end up with more favorable outcomes than older children (16). In the current study, 11% of children had experienced recurrent AIS and the rate of TIA before the AIS had been 8.2%. Recurrent arterial ischemic stroke (AIS) is recognized as a significant cause of mortality and morbidity in the children. (21). There are multiple risk factors for AIS, but the only confirmed risk factor is the presence of vasculopathy, and particularly moyamoya disease (21).

5- CONCLUSION

With careful investigation, in most of the children underlying risk factors could be found. Based on the results, acute illness and cardiac disorders were the most frequent risk factors in pediatric stroke. However, some of these risk factors (such as anemia, infection, and dehydration) which are relatively common in the pediatric population were preventable.

6- CONFLICT OF INTEREST: None.

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