J Pediatr Rev. 2018 July; 6(2):e58356. doi: 10.5812/jpr.58356.

Published online 2018 April 28. **Case Report and Review of Literature**

Pediatric Stroke in Southern Iran; Clinical Presentations, Etiologies and Outcomes: A Case-Series and Review of Literature

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Received 2017 July 20; **Revised** 2017 October 21; **Accepted** 2017 November 04.

Abstract

Background: Pediatric stroke is defined as rapid developing clinical signs of focal (or global) disturbance of cerebral function without any apparent cause other than of vascular origin lasting for 24 hours or longer in the ages of 1 month to 18 years. It is relatively rare in children, however, it can lead to significant mortality and morbidity.
Objectives: The present study aimed to identify clinical presentations, etiologies, and outcomes of pediatric stroke in southern Iran.
Methods: This case-series study included all patients that were diagnosed with a pediatric stroke and admitted to the Pediatric Neurology ward at Namazi hospital in Shiraz, Iran, from May 2009 through March 2012.
Results: During the study period, 40 newly diagnosed patients (27 males and 13 females) between the ages of 10 months and 18 years old were identified. The most prevalent referring symptoms were hemiparesis and hemiplagia (65%), seizures (45%), speech difficulties (42.5%), and altered mental status (35%). A known single etiology was identified in 82.5% of patients. The most common single risk factor was cardiac abnormalities with 30% frequency, followed by idiopathic and vascular with 17.5%. The outcome of pediatric patients revealed incomplete recovery with moderate neurological deficits (45%) including residual epilepsy (15%), speech difficulties (15%), and behavioral dysfunction (7%), which indicate their need for help in some of their daily activities.
Conclusions: Stroke in southern Iranian pediatric patients demonstrated different patterns of causes and risk factors with similar clinical presentations and outcomes.

Keywords: Stroke, Risk Factor, Children, Adults, Iran

1. Background

Stroke is one of the major reasons of adult death in the developing world as well as an important cause of mortality and chronic neurological morbidities in children (1). It is a neurological injury caused by the occlusion or rupture of cerebral blood vessels and can be ischemic, hemorrhagic, or both in the artery or vein.

Ischemic stroke is usually caused by arterial occlusion; however, it may also be caused by venous occlusion of cerebral sinuses. Hemorrhagic stroke is the result of bleeding from ruptured cerebral artery. However, it may be seen due to bleeding into the site of an acute ischemic stroke.

According to the world health organization (WHO) definition, stroke is rapidly developing clinical signs of focal (or global) disturbance of cerebral function due to no apparent cause other than of vascular origin, and symptoms lasting 24 hours or longer or leading to death (1). Stroke from the age of one month to 18 years is called Pediatric Stroke. Its incidence is reported from 2.3 - 2.7 per 100,000 in North America (2, 3) to 13 per 100,000 in France (4). Stroke is gaining more study interest in the pediatric age group nowadays due to its grave squeal and costs, and its impact on personal life and society. Roughly 10% - 25% of children with a stroke will pass away, up to 25% of them experience recurrence, and up to 66% develops persistent neurological deficits or subsequent seizures disorders, learning or developmental problems (5). While high blood pressure, diabetes, and atherosclerosis are common causes of adult strokes, they are rare in children. Common risk factors for stroke in children include cardiac diseases, infection, metabolic disorders, and vasculopathy (6, 7). Multiple risk factors are often present in as many as 25% of children with stroke, which means further investigations are warranted even when one risk factor has been identified (8). As in

adults, pediatric stroke can be ischemic or hemorrhagic; although ischemic stroke is more common, prevalence is variable (7, 9). Despite an increased recognition of stroke in children in recent years, there is often a delay in diagnosis and many cases may still remain under or misdiagnosed. Key points in the diagnosis of pediatric stroke are prompt physical examination, laboratory tests, and radiologic studies. Urgent brain CT scan is recommended for children with any neurologic symptoms of acute focal neurological deficit, aphasia, or reduced level of consciousness (3). Magnetic resonance imaging (MRI) in suspected stroke should be considered only if it is available within one hour of arrival at the hospital. It should be provided to both groups of ischemic and hemorrhagic stroke for improved diagnostic resolution, or if the initial CT scan is negative and a stroke is still suspected. Magnetic resonance angiography (MRA) and magnetic resonance venography (MRV) could more accurately define the site of an arterial or venous occlusion. CT angiography (CTA) is an accurate means of identifying primary vascular abnormalities when there is an unexplained hemorrhagic lesion (3, 10). A prompt and precise diagnosis of pediatric stroke, associated to an effective management of vascular emergencies, is a crucial point to reach a correct therapy and, consequently, a positive outcome.

2. Objectives

The present study was designed to describe the etiologies, clinical presentations, and outcomes of pediatric stroke patients admitted to the Pediatric Neurology ward at Namazi hospital, Shiraz, Iran.

Table 1. Age Distribution of Patients with Stroke

Age	Frequency (%)
1 mo - 6 y	19 (47.5)
6.1 - 12, y	11 (27.5)
12.1 - 18, y	10 (25.0)

3. Materials and Methods

We identified patients in the pediatric age group with a stroke who were admitted to the pediatric neurology ward, at Shiraz Namazi hospital in southern Iran, from May 2009 to March 2012. This hospital is the largest tertiary medical center affiliated to Shiraz University of Medical sciences.

The data including the patient's demographic characteristics, clinical presentations, physical examinations and results of the blood tests at onset of first stroke, and outcomes were recorded. Patients with onset of stroke in the perinatal or neonatal period were excluded.

Children were considered as stroke in the beginning based on the clinical presentation and the results of initial brain neuro-imaging studies (brain MRI or CT scan). However, MRA, MRV, and sometimes CT angiography were considered for definite diagnosis. The usual investigations for stroke in our center included cardiac evaluation, coagulation studies, complete blood count, and prothrombotic states screening (protein C, protein S, antithrombin III, plasminogen, Factor V Leiden, antinuclear antibody (ANA), anticardiolipin antibody levels), which were done for all patients. However, MRA, MRV, CT, or four vessel angiography were done if indicated for further diagnosis and management. In addition, all patients had blood culture, cerebrospinal fluid analysis, and metabolic survey including liver and renal function tests, blood glucose, lactate, and lipid profile. Investigations for neuro-metabolic disorders were done only if there was an indicator in the patient's history, physical examination, or brain neuro-imaging suggesting a metabolic disorder. Gene analyses for neuro-metabolic disorders were not performed in this study.

Patients had a follow up examination up to 12 months after the event and was classified based on its result to four categories: I: completed recovery, II: incomplete recovery with mild neurological deficit, III: incomplete recovery with moderate neurological deficit, and IV: incomplete recovery with severe neurological deficit. Deceased patients were considered as group V.

Data were collected through the chart review at presentation and subsequently at follow up of the patients. The study was approved by the research ethics committee of Shiraz University of Medical Sciences, school of Medicine. The study was waived from consent, however the patients' information remained confidential.

4. Results

During the study period, 40 patients consisting of 27 male and 13 female (M/F: 2/1), age range between 10 months to 18 years were diagnosed as a stroke. Table 1 shows the age characteristic of the patients.

Hemiparesis and hemiplegia, seizures, speech difficulties, and altered mental status were the most prevalent presenting symptoms with 65%, 45%, 42.5%, and 35%, respectively. Hemiplegia with muscle weakness was detected on the right side in nine patients and on the left side in 17. Radiographic studies showed previous old lesions indicating of a silent stroke in 4 patients. Four patients (10%) were diagnosed as cerebral venous thrombosis and the remaining (90%) had ischemic and or hemorrhagic events that occurred in cerebral arteries.

Patients were evaluated using history, presenting signs and symptoms, physical examination, and para-clinical

Table 3. Different Etiologies in Pediatric Patients Diagnosed as Stroke

Risk Factor	Frequency	%
Cardiac	13	32.5
Vascular	8	20
Infection	3	7.5
Neurometabolic syndrome	4	10
Chronic kidney diseases and hypertension	2	5
Vasculitis	2	5
Trauma	1	2.5
Idiopathic	7	17.5

Table 4. Prognosis of Patients with Brain Stroke, 12 Months After the Event[a]

Outcome Category	Frequency	%
I	5	12.5
II	18	45
III	9	22.5
IV	2	5
V	2	5
VI	4	10

[a] I, Complete recovery; II, incomplete recovery with mild neurological deficits (patients can do his /her routine daily activity independently); III, incomplete recovery with moderate neurological deficit (patient needs help for some of his/her daily activities; IV, incomplete recovery with severe neurological deficits (patients do no physical activity and completely dependent on others); V, death; VI, lost from follow up.

studies. Table 2 shows the summary of data derived from the patients of our study.

A known etiology for stroke was identified in 33 (82.5%) patients. Multiple risk factors were detected in five patients, one of them with three risk factors. The most common known single risk factor was congenital heart diseases that was seen in 13 patients (30%) with Tetralogy of Fallot the most frequent one. However, stroke as a post cardiac surgery complication was seen in two patients and only one case suffered from septic endocarditis. In groups with vascular risk factors, eight cases were identified; two of them were diagnosed as Moyamoya disease and the other two Moyamoya syndrome. The remaining (four patients) were considered as cerebral vasculopathy. Investigations for neurometabolic disorders, including serum lactate and amino acids, urinary organic acids, and the homocysteine level were performed for 7/40 patients. However, the result was positive in four out of 40 patients (two with homocysteinemia and two with mitochondrial encephalopathy).

Three patients with bacterial meningitis, viral meningoencephalitis, and varicella infection consisted the group of infectious risk factors. Although two patients showed Protein-C deficiency condition, one of them associated with thalassemia intermedia, and the other with chronic idiopathic purpura, they were not considered as the single precipitating risk factors of hematologic groups due to their association with Moyamoya syndrome. In spite of all investigations, no risk factor was identified in seven patients (17.5%).

Table 4 shows the outcome of patients 12 months after the event. Clinical recurrence occurred in one patient three months later, which resulted to death. No patient died during the first admission, however, two of them died at the end of the 12 months follow up. One of them passed due to clinical recurrence of stokes that involved critical areas of the brain, which was incompatible with life, and the other due to severe chest infection. Four patients were lost from the follow up at the end of the year.

Residual epilepsy at the last follow up visit was present in 6 patients (15%) and residual speech difficulty in 6 patients (15%), whereas, residual behavioral dysfunction including decrease school performance, lack of eye contact, and severe aggression was present in three patients (7%).

5. Discussion and Review of Literature

This study indicated that stroke in southern Iranian children demonstrated different patterns of causes and risk factors with similar clinical presentations and outcomes. Frequency of stroke among patients under one month to five years old, 6.1 - 12 years and 12.1 - 18 years was 47.5%, 27.5%, and 25.0%, respectively. The most prevalent symptoms in stroke patients were hemiplegia (65%), seizures (45%), speech difficulties (42.5%), and altered mental status (35%). Cardiac failure, hematological disorders, infection, neuro-metabolic syndromes, trauma, chronic kidney diseases, hypertension, and thrombophilia were identified as the predisposing causes of stroke. Cardiac abnormalities were the most important risk factors in stroke patients with 32.5% frequency.

Pediatric stroke has a sudden onset followed by rapidly developing clinical signs and symptoms of cerebral dysfunction due to vascular compromise lasting for at least 24 hours. It has significant morbidity and mortality and may happen at any age from one month of age to 18 years old. The type of stroke also varies according to age. In Western countries, 80% to 85% of strokes among adults are ischemic and the rest are hemorrhagic. While in children, 55% of strokes are ischemic with the remainder being hemorrhagic (6). In the present study, stroke was mostly seen in the age of one month to five years. The age range was different from the previous report from Iran, which was two to five years. It could be due to a high level of suspicious to pediatric stroke in recent years compared to before (11). Fullerton and colleagues estimated that the stroke incidence is 2.3 per 100,000 children per year (1.2 per 100,000 per year for ischemic lesions and 1.1 per 100,000 per year for hemorrhagic lesions) (3). A study of Chinese children in Hong Kong found a similar overall stroke risk (2.1 per 100,000 per year), however, only 28% of those had hemorrhagic strokes (12). Nevertheless, this number was reported 1.8 per 100,000 from Northeast of Iran (13). The peak age for both types of stroke is reported to be the first year of life, with a third of the cases presenting in this age group, whereas subarachnoid hemorrhage (SAH) is more common among teenagers (6, 14). The clinical manifestation of stroke is extremely various, depending on age, cause, and involved vascular territory (15). Hemiparesis, seizure, language, and speech difficulty were the more common presentations in our series. These findings were similar to other reports (16-18), in up to 80% - 94% of cases with an ischemic type of stroke (6, 14), while headaches, altered mental status, or vomiting are the most likely to occur in hemorrhagic types (8).

Similar to previous studies, it was observed that the etiology of stroke was known in almost 80% of our patient series. Previous studies reported the main causes of stoke in 57% to 88% of patients (11, 13, 14, 16). Identification of risk factors plays an important and crucial role in the management of stroke, due to the fact that the majority of signs and symptoms of a stroke are nonspecific, and can be easily attributed to other causes. Identification of risk factors may be an effective way to avoid delaying in diagnoses that would prompt more aggressive and timely investigation. It is reported that in 80% of pediatric patients with stroke recurrence, a definite risk factor was identified. Multiple risk factors are often involved in as many as 25% of children with stroke, which means further studies are needed to identify them. The most common etiologies for stroke reported in the literature were cardiac and hematological diseases. The result of the present study also described the same results. The most common risk factor in our series was cardiac disorders (32.5%), which is almost close to the results of the study in the Chinese population (2, 12), while this number was reported nearly as twice from the previous studies in Iran (11, 13). On the other hand, Masri and coworkers indicated that neurometabolic disorders were the main causes of strokes in Jordanian children (16). They indicated the importance of inherited disorders in Jordan (7, 16, 17). Although neurometabolic disorders as etiologies of stroke are amongst the rarest, they are well reported in the literature from regions with high rate of consanguineous marriages (18). As we have seen, this rate was 10% in this series, which is relatively high compared to other risk factors. We did not observe any cases of sickle cell diseases, which is known to increase the risk of stroke to 200 - 400 fold (3). The most common hemoglobinopathy in Iran is Thalassemia syndrome. However, there was just one patient with thalassemia intermedia in our study who experienced a recurrent stroke, according to neuroimaging studies, and suffered from coagulopathy disorders as well. Although we have not evaluated prothrombotic disorders as the primary risk factors in our study, they were found in patients with congenital heart disease due to hypoxia, cyanosis, polycythemia, as well as a patient with nephrotic syndrome as well. In a systematic review, Haywood et al., found that all of the investigated thrombophilia factors were more common in children with the first acute ischemic stroke than in healthy children, particularly for protein C deficiency and the MTHFR C677T mutation (19). Therefore, researchers suggested a prothrombotic workup in all the suspected pediatric cases suffering from acute ischemic stroke (3, 5, 7, 8, 18, 20).

The outcome of pediatric patients revealed incomplete recovery with mild neurological deficits (45%) including residual epilepsy (15%), speech (15%), and behavioral disorders (7%). These outcomes are better compared with the findings of previous reports (3, 7, 15, 16, 18). Although, the survivors appear to have higher levels of functioning with mild neurological deficit, these patients and their family experience a high level of stress. Decreased school performance, low learning ability, behavioral problems, and physical disabilities could be a heavy burden on both children and their families during their routine daily activities.

Although the current sample of 40 cases of stroke among southern Iranian children demonstrated different patterns of causes and risk factors, compared with those for other ethnic groups, patients exhibit similar clinical presentations and outcomes compared with previous studies. This indicated the timely and precise identification of risk factors associated with poor outcomes.

Given that there were some limitations to this study, including the relatively small number of patients and

lack of additional studies such as gene analysis and long-term follow-ups, we suggest international and collaborative stroke studies among children using standard protocols to identify risk factors and to determine the treatments modalities.

Acknowledgments

This article was based on Zahra Foroughi Nia's thesis for her medical degree, number 2113-01-01-89 from Shiraz University of Medical Sciences, school of Medicine.

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Table 2. Summary of Data on 40 Pediatric Patients with Stroke

No.	Age	Sex	Clinical Presentation	Etiology/ Risk Factors	Outcome
1	9	M	Upper extremity weakness	TOF	Mild disability
2	13	M	Decreased level of consciousness, seizure	Hyperoxaluria, hypertension, chronic kidney diseases	Severe disability, lost F/U
3	4	F	Right side hemiplegia, speech difficulty	TGA,VSD, PH	Mild disability
4	16	M	Left side hemiplegia, speech difficulty	Unknown	Complete recovery, lost F/U
5	18	M	Right side hemiplegia +speech difficulty	TOF, BT-shunt, septic endocarditis	Mild disability
6	5	M	Speech difficulty	Unknown	Complete recovery
7	18	F	Speech difficulty, seizure, behavior problems	Moyamoya disease	Moderate disability
8	9	M	Speech difficulty, right side hemiplegia, seizure, fever	Meningitis	Mild disability
9	16	M	Seizure, right side hemiplegia, Speech problem	Vasculopathy	Mild disability
10	4	M	Left side hemiplegia, decreased level of consciousness, speech difficulty	PA, VSD	Mild disability
11	8	M	left side hemiplegia, seizure, Speech difficulty	Vasculopathy	Mild disability
12	3.5	M	left side hemiplegia, seizure	Mitochondrial diseases	Mild disability
13	16	M	Ptosis+ right side hemiplegia	Vasculopathy	Mild disability
14	4	M	Decreased level of consciousness, seizure	uncontrolled status epilepticus, Behcet syndrome	Complete recovery
15	2.5	F	left side hemiplegia, decreased level of consciousness, speech difficulty	TOF (post cardiac surgery)	Mild disability
16	2	M	left side hemiplegia, speech difficulty	Unknown	Mild disability
17	0.8	M	Left side hemiplegia	TOF	Mild disability
18	7	M	Right side hemiplegia	VSD (post cardiac surgery)	Mild disability
19	10	F	Left hemiplegia	Moyamoya disease	Moderate disability
20	16	M	Right side hemiplegia, decreased level of consciousness, seizure, speech difficulty	Encephalitis, venous thrombosis	Complete recovery
21	3	M	Right side hemiplegia, speech difficulty	Post chicken pox infection	Complete recovery, lost F/U
22	2.5	F	Left side hemiplegia, decreased level of consciousness	VSD, PH, PS	Mild disability
23	1.5	M	Seizure, speech difficulty	Nephrotic syndrome, venous thrombosis	Moderate disability
24	3	F	Seizure, decreased level of consciousness	VSD, PH	Complete recovery
25	8	M	Headache, decreased level of consciousness	Unknown	Severe disability, lost F/U
26	11	M	Left side hemiplegia, visual disturbances	Chronic ITP, protein- C deficiency, Moyamoya syndrome	Died
27	7	M	Left side hemiplegia, headache, vomiting	Post- trauma	Moderate recovery
28	1	M	Status epilepticus, decreased level of consciousness	TGA, VSD	Moderate disability
29	1	F	Left side hemiplegia	Unknown	Complete recovery
30	1.5	M	Left side hemiplegia	TOF, BT-shunt	Moderate recovery
31	16	F	Decreased level of consciousness, seizure, speech difficulty	Vasculopathy	Mild disability
32	2	F	Right side hemiplegia, speech difficulty	Thalassemia intermedia, protein- C deficiency, Moyamoya syndrome	Mild disability
33	2.5	M	Left side hemiplegia	TA, VSD, ASD	Moderate disability
34	17	M	Left side hemiplegia, seizure, behavior problems	Unknown	Mild disability
35	11	F	Left side hemiplegia	TGA, VSD, PH	Mild disability
36	10	F	Decrease level of consciousness, seizure	Unknown	Moderate recovery
37	5	F	Speech difficulty, seizure	Mitochondrial diseases	Moderate disability
38	3	M	Left side hemiplegia, decreased level of consciousness, seizure	Polyarthritis nodosa	Severe disability
39	13	F	Headache, decreased level of consciousness, visual disturbances	Homocysteinemia	Death
40	8	M	Decreased level of consciousness, seizure	Homocysteinemia	Severe disability

Abbreviations: ASD, Atrial Septal Defect; BT-shunt, Blalock-Taussig Shunt; F, Female; ITP, Idiopathic Thrombocytopenic Purpura; M, Male; PA, Pulmonary Atresia; PH, Pulmonary Artery Hypertension; PS, Pulmonary Stenosis; TA, Tricuspid Atresia; TGA, Transposition of Great Arteries; TOF, Tetralogy of Fallot; VSD, Ventricular Septal Defect.