INCIDENCE AND ETIOLOGY OF PEDIATRIC STROKE IN SOUTHERN KHORASAN

K Ghandehari[(1)], Z Izadi-Mood[(2)]

Abstract

INTRODUCTION: Ischemic stroke is rarely seen in childhood. The pediatric causes of stroke are very different from adult causes.

METHODS: This population-based study was conducted to determine the incidence, clinical manifestations and etiology of pediatric ischemic stroke in Southern Khorasan, Iran, during 2002-2007. In this province, every child with possible diagnosis of stroke is referred to a stroke neurologist and routinely admitted to the Pediatric Division of Vali-e-Asr tertiary care hospital. The diagnosis of ischemic stroke was made based on the clinical presentation and brain imagery. All of the patients underwent a standard battery of diagnostic investigations.

RESULTS: Seventeen children with ischemic stroke (7 girls, 10 boys) were evaluated. The incidence of pediatric ischemic stroke in Khorasan province is 1.8 cases per 100,000 children population per year. Meningoencephalitis-induced vasculopathy constituted 23.5% of the etiology followed by Fallot tetralogy, head trauma, dehydration, migraine, and hypercoagulable state. 23.5% of our patients had uncertain causes of stroke. In-hospital mortality of our pediatric ischemic stroke patients was 11.7%.

CONCLUSIONS: The incidence and clinical characteristics of pediatric brain infarction in Iran are the same as in other studies. Meningoencephalitis-induced vasculopathy is the most common determined etiology of pediatric ischemic stroke in Southern Khorasan.

Keywords: Child, stroke, incidence, etiology.

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Introduction

Stroke is rarely seen in childhood. Hemiplegia secondary to vascular disorders occurs in children with an incidence of 1-3 cases per 100,000 population per year.[1] Congenital stroke may pass unrecognized by parents during early infancy, until the child starts crawling or walking when asymmetry is noted, or delay in the rate of acquired motor or cognitive skills is manifested. Many parents do not realize that children may also suffer stroke. The risk factors of stroke and its frequency are different in children and adults; e.g. atherosclerosis is a rare cause of brain infarction in children[1]. Certain subgroups of children are at high risk of ischemic stroke; these include children with congenital heart disease, sickle cell anemia, cancer, Moyamoya disease and Down syndrome.[1] Homocystinuria, mitochondrial disease, prothrombotic states and trauma are among other causes of ischemic stroke in childhood and early adolescence.[1,2] Some children have more than one factor contributing to the cause of their stroke.[2] Epidemiologic studies of pediatric stroke in Iran are lacking. This study was conducted to evaluate the incidence, clinical presentation and etiology of pediatric brain infarction.

Materials and methods

This population-based study was carried out in Southern Khorasan Province, Iran, with a total population of 682,000, including 196,000 children aged less than 15 years (41% females, 59% males). In this province, all children with possible diagnosis of ischemic stroke are referred to stroke neurologists and routinely admitted to the Pediatric Division of Vali-e-Asr tertiary care Hospital.

(1) Kavian Ghandehari, MD, FLSP, Associate Professor of Neurology, Mashhad University of Medical Sciences, Iran.
Email: *kavianghandehari@yahoo.com*
(2) Zahra Izadi-Mood MD. Assistant Professor, Pediatrics Dept, Vali-e-Asr Hospital, Birjand, Iran.

Corresponding author: Kavian Ghandehari MD.

Signed informed consent was obtained from the parents. Consecutive children hospitalized with mild and severe ischemic stroke were enrolled in the study. Patients transferred to other medical centers, those who died before complete investigation, and patients with vasospasm after subarachnoid hemorrhage were excluded.

Data on demographics, clinical presentation, and investigations conducted on these patients were registered in Southern Khorasan Stroke Data Bank during 2002-2007 and entered in SPSS9 software package. Stroke was defined as an ischemic focal neurological deficit persisting for at least 24 hours.[3] A hypodense infarct area compatible with a definite vascular territory was considered as the neuroimaging criteria of ischemic stroke.[3] Stroke onset was categorized as sudden, acute and subacute.[4]

Sudden onset and acute onset were defined as seconds up to a few minutes, and within a few days, respectively. Clinical findings were systematically evaluated. Motor and sensory deficits were classified as complete or partial.

The presence of aphasia, hemineglect and visual field defect was evaluated whenever possible according to the child's age.[4] Seizure, fever, headache, and altered consciousness were recorded.[4] All of the ischemic stroke patients underwent a standard battery of diagnostic investigations,[5] which included brain CT, electrocardiography (ECG), blood count and differential, measurement of blood electrolytes, ESR, CRP, fasting blood sugar, blood culture, assessment of coagulation profile and lipid profile, and transthoracic echocardiography.[5] 24-hour Holter monitoring and transesophageal echocardiography were performed in subjects with non-diagnostic ECG and/or transthoracic echocardiography despite high suspicion of cardioembolism.[5] Brain MRI was requested in pediatric patients with brain infarction and normal CT. MRA was performed in suspected arterial dissection, vasculitis, vasculopathy, arteriovenous malformation, Moyamoya disease or aneurysm.[5,6]

An extended coagulation profile (antithrombin III, protein C, protein S) was obtained, VDRL and HIV tests were performed and antinuclear and anticardiolipin antibodies, homocysteine and lactate were measured in pediatric patients without any identifiable cause of stroke.[5,6] EEG was performed in patients presenting with seizure.[6]

Lumbar puncture was carried out in febrile patients suspected of meningitis- or encephalitis-induced vasculopathy.[6]

The cerebrospinal fluid analysis included protein, sugar, cell count, bacteriology and polymerase chain reaction for herpes virus.[5,6] Serologic tests for brucellosis and toxoplasmosis were requested in febrile patients. Ultrasound Doppler of neck arteries was requested in children with atherosclerosis risk factors such as diabetes, hypertension and hypercholesterolemia.[7]

These differential levels of assessment are the standard protocol in diagnostic work-up of stroke patients and do not influence the etiologic diagnosis.[5,7] Incidence was defined as the number of new cases of a disease which came into existence within a certain period of time per specified unit of population.[8]

The population at midpoint in the time period was picked to represent the average population at risk. In this prospective study, 1.96×100,000 was used as person-years denominator in the calculation of cumulative incidence rate. The study was approved by the Ethics Committee of Vali-e-Asr Hospital.

Results

According to clinical presentation, twenty children were suspected of having brain infarction. However, eighteen cases of pediatric ischemic stroke were identified during the 5-year period. One patient died before complete diagnostic investigations and was excluded.

The remaining 17 cases (7 female, 10 male) with a mean age of 5.5 years were investigated. All of these patients resided in Southern Khorasan Province, Eastern Iran with a child population of 196,000.

The incidence of childhood ischemic stroke in our province is 1.73 cases per 100,000 children population per year. The incidence was calculated as:[8] A/B=1.73. A=number of new cases of pediatric ischemic stroke per year; 17/5=3.4. B=child population/100,000; 196,000/100,000=1.96.

This incidence includes congenitally malformed and normal children.

The real incidence of childhood ischemic stroke, including the one excluded patient is 1.83 cases per 100,000 child population per year. The real incidence is calculated as A/B=1.83 per 100,000 child population, where A is the total number of new cases of pediatric ischemic stroke per year.

TABLE 1. Clinical characteristics, etiology and topography of 17 cases of pediatric brain infarction

Case No.	Sex	Age (Year)	Clinical manifestations	Etiology	Vascular territory
1	F	1.5	Fever, generalized seizure, right hemiparesis**	Fallot Tetralogy	cortical and deep MCA
2	M	0.6	Right hemiplegia	Uncertain	cortical MCA
3	F	0.7	Left hemiparesis, left sided seizure	Head trauma	deep MCA
4	M	1.2	Left hemiparesis	Uncertain	cortical PCA, Thalamus
5	M	0.7	Fever, right sided seizure, right hemiplegia	CNS infection	cortical PCA, Thalamus
6	F	2.2	Right hemiparesis, aphasia	Head trauma	deep MCA
7	M	2.5	Fever, generalized seizure, left hemiplegia*	Dehydration***	cortical and deep MCA
8	M	2	Fever, right-sided seizure, right hemiparesis	CNS infection	cortical MCA
9	F	3	Fever, generalized seizure, left hemiparesis*	CNS infection	cortical and deep MCA
10	F	3	Fever, left-sided seizure, left hemiparesis	CNS infection	cortical MCA
11	M	3	Right hemiplegia, aphasia	Fallot tetralogy	cortical ACA
12	F	8	Right hemiplegia	Uncertain	deep ACA
13	M	9	Right sided seizure, right hemiparesis	Dehydration***	cortical MCA
14	F	11	Left hemiparesis	Migraine	cortical MCA
15	M	12	Right hemiparesis, aphasia	Uncertain	cortical MCA
16	M	14	Right hemiparesis, right hemihypoesthesia****	Prothrombotic	Lacune, MCA
17	M	14.9	Right hemiparesis, right hemihypoesthesis	Migraine	cortical MCA

* Deceased, ** Down Syndrome, *** Post gastroenteritis dehydration, **** Protein C deficiency

TABLE 2. Frequency of etiologies of pediatric brain infarction in four developing countries

Etiologic subgroup	Iran (No: 17)	Turkey[23] (No: 57)	Saudi Arabia[12] (No: 79)	India[13] (No: 31)
Congenital heart disease	11.8%	24.5%	7.6%	19.4%
Infectious disease	23.5%	-	20.2%	22.6%
Head trauma, arterial dissection	11.8%	-	3.8%	25.7%
Prothrombotic state, hematologic disease	5.9%	15.8%	37.1%	12.9%
Moyamoya, cerebrovascular anomaly	-	12.3%	8.8%	6.5%
Systemic vasculitis	-	-	1.2%	-
Dehydration	11.8%	-	2.5%	-
Hyperhomocysteinemia	-	3.5%	-	-
Inherited metabolic disease	-	1.8%	5%	-
Migraine-induced stroke	11.7%	-	-	-
Uncertain	23.5%	42.1%	13.8%	12.9%

Table 1 represents demographics, clinical characteristics, etiology and vascular territory of our pediatric patients with brain infarction. Unilateral weakness was found in all of the patients; however, ipsilateral extensor plantar response and heightened deep tendon reflexes were found in 41% and 35% of the patients, respectively.

Seizure, fever and altered consciousness were present in 47%, 35% and 23% of the patients, respectively. The onset of pediatric brain infarction in our study group was sudden in 35%, acute in 59% and subacute in 6% of cases.

Topography of infarction was determined by brain CT scan in 70.6%, and MRI in 29.4% of the cases. The infarctions were located in the carotid territory in 88% of the cases. Meningoencephalitis-induced vasculopathy constituted the most common determined etiology of pediatric stroke in our province (23.5%). All of these cases were young children and half were referred from a rural area in summer 2004.

The polymerase chain reaction for herpesvirus was negative in these four patients; however, special virology facilities were not available.

Bacterial meningitis and encephalitis including neurotuberculosis was ruled out in cerebrospinal fluid (CSF) smear analysis and culture. These cases were classified as unspecified meningoencephalitis.

23.5% of our pediatric stroke patients had uncertain causes of brain infarction. In-hospital mortality of our pediatric ischemic stroke patients was 11.7%.

Discussion

Our hospital is the only one in our province to have Neurology and Pediatric Divisions which deal with pediatric stroke patients.

This helped to minimize selection bias, maximize accuracy in stroke diagnosis, and allow uniform evaluation of children with brain infarction.[4]

There is some variation among epidemiologic studies on the inclusion of neonates, and whether to use 16 or 18 as the age cut-off for pediatric stroke.[1,2]

The incidence of pediatric brain infarction in our province is similar to the annual incidence of 2.5 and 4.5 cases per 100,000 children population per year in Minnesota[9] and Texas,[10] respectively, which include ischemic and hemorrhagic stroke. The incidence of stroke in the pediatric population is estimated at 2-3 per 100,000 population in developed countries.[11]

The incidence of pediatric ischemic stroke in Saudi Arabia and India is reported at 20 cases and 8 cases per 100,000 pediatric population, respectively,[12,13] which is significantly higher than in developed countries. Seizure was a cardinal manifestation of pediatric brain infarction in 47% of our study group. Seizure was present in 64% of our stroke patients aged ≤3 years. Other studies have reported seizure in up to 80% of neonates with ischemic stroke,[1,2] however, none of our patients were neonates. Hemiplegia and focal signs were found in all cases in our pediatric stroke group.

The immature central nervous system may not demonstrate focal signs, until the child is more than 6 months of age.[1] All of our pediatric strokes were found in children older than 6 months. Children with sickle cell anemia,[14]

Moyamoya disease[15] and antiphospholipid antibody[16] are highly susceptible to brain infarction. These causes of stroke were not found in our study group. The etiologic frequency of pediatric brain infarction is different around the world; e.g. cyanotic heart disease and sickle cell anemia are the most frequent causes of pediatric stroke in Brazil.[17]

Moyamoya disease is a frequent cause of pediatric stroke in Japan[15]. Cyanotic heart disease constituted 11.7% of the causes of pediatric stroke in our study. Cyanotic heart disease was found in 11% and 10% of French and American children with brain infarction, respectively.[18,9] Rheumatic valvular disease (RVD) is a common cause of stroke in the adult population of Iran and other developing countries.[19]

Etiologic evaluation of ischemic stroke in young Iranian adults revealed that RVD is present in 32% of young Iranian adults with brain infarction.[20] RVD was found in all young Iranian adults with ischemic stroke and atrial fibrillation.[20] Surprisingly, RVD was not found in our pediatric ischemic stroke patients.

Meningoencephalitis-induced vasculopathy is the most common determined etiology of pediatric brain infarction in our study.

Intracranial vasculopathy secondary to meningitis and encephalitis constituted 57% of the causes of pediatric brain infarction in Pakistan.[21] 78% of Pakistani pediatric strokes due to intracranial infections occurs in children below five years of age.[21]

Infectious diseases constituted 15% and 22% of the causes of pediatric ischemic stroke in Saudi Arabia and India, respectively.[13,22]

Infectious etiologies were not found is Turkish children with stroke.[23]

Table 2 compares the frequency of etiologies of pediatric ischemic stroke in four developing countries. Pediatric brain infarction is being increasingly reported in children with history of Chickenpox in Toronto population,[24] however, none of our patients had history of Chickenpox.

Migraine-induced stroke constituted 11.7% of etiologies in our study group and 33% of causes of brain infarction in our older children. Most cases of migraine-induced stroke occur in patients with non-hereditary hemiplegic migraine.[25]

The incidence of pediatric brain infarction in Southern Khorasan is similar to that in developed countries. Meningoencephalitis-induced vasculopathy is the most common determined cause of pediatric ischemic stroke in Southern Khorasan.

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