

THE CAUSES AND NEUROIMAGING FINDINGS IN PEDIATRIC ARTERIAL ISCHEMIC STROKE

Shaila Ali, Muhammad Zia Ur Rehman, Tipu Sultan

Children's Hospital and Institute of Child Health Lahore Pakistan

ABSTRACT

Objective: To determine the causes of arterial ischemic stroke and neuroimaging findings in children.

Study Design: An observational, prospective, cross-sectional study.

Place and Duration of Study: Department of Paediatric Neurology, Children's Hospital & Institute of Child Health, Lahore for a period of six months from Nov 2014 to Apr 2015.

Material and Methods: Children from 1 month to 18 years of age with radiologically confirmed arterial ischemic stroke, occurring 1st time in life, were included in the study. Arterial ischemic stroke (AIS) was confirmed on the basis of history, examination and neuroimaging findings of the brain. Further investigations were done according to the cause of arterial ischemic stroke and neuroimaging brain findings.

Results: A total of 72 patients of arterial ischemic stroke were identified over a period of 6 months. Among these, male predominance was found in 53 (73%) children. Outpatient department patients outnumbered the indoor patients with stroke in 38 (53%) children. Children between 1-5 years of age were the most affected ones (65%). Hemiplegia, fits, hemiparesis and aphasia were the most common presenting features affecting 60 (83%), 27 (38%), 14 (19%) and 8 (11%) children respectively. The commonest cause of arterial ischemic stroke was iron deficiency anemia, found in 30% (n=22) of the children followed by anemia due to other causes in 27% (n=20) and congenital heart diseases in 8.3% (n=6) of the children. On neuroimaging studies, parietal lobe was the most affected part of the brain in 23% of the children (n=16). Middle cerebral artery was the major artery affecting 57% (n=12) of the patients.

Conclusion: Iron deficiency anemia, anemia due to other causes and congenital heart diseases were common etiologies in children with arterial ischemic stroke in our study. Parietal lobe and middle cerebral artery were the most affected areas of the brain on neuroimaging.

Keywords: Aphasia, Arterial ischemic stroke, Hemiparesis, Hemiplegia, Iron deficiency anemia, Neuroimaging.

This is an Open Access article distributed under the terms of the Creative Commons Attribution License (<http://creativecommons.org/licenses/by/4.0>), which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.

INTRODUCTION

Pediatric stroke is defined as an acute focal neurological deficit in a child lasting for >24 hours until proven otherwise. It can be ischemic or hemorrhagic depending on the cause. The ischemic varieties include arterial ischemic stroke (AIS) and cerebral sin venous thrombosis. The AIS is the focal ischemic brain injury leading to infarction due to occlusion of anterior, middle or posterior cerebral arteries or their branches. In hemorrhagic stroke there is intracranial hemorrhage without trauma¹.

Childhood arterial ischemic stroke is one of the serious and important causes of morbidity

and mortality. Cerebrovascular accident (CVA) is the 10th leading cause of death in children in United States. Each year 1 in 4,000 newborns and 2000 older children are affected by stroke². The incidence of AIS annually among infants in children ranges from 0.63 to 7.9/100,000 children per year³. Over the past few decades, the incidence of stroke has become twice in low and middle income countries and has dropped to 40% in high income countries³⁻⁴. World health organization (WHO) carried out measurements including two important parameters of age and gender affecting the incidence and mortality rates of stroke. There was more than 10 fold difference in both parameters among different countries. Both were higher in low income countries (North Asia, Eastern Europe, Central Africa and South Pacific) as compared to high income countries

Correspondence: Dr Shaila Ali, House No 15, Al-Razzaq Villas, Madhali Road Sahiwal Pakistan (Email: dr_alishaila@hotmail.com)

Received: 14 Jun 2017; revised received: 01 Nov 2017; accepted: 27 Nov 2017

(Western Europe, North America)⁴ Stroke incidence varies with age as infants are highest to be affected than children⁵. Non-Asian and white children were at lower risk of AIS than Asian and black children⁶. Similarly male children are at greater risk than female^{3,6}.

The main causes of AIS in children are congenital and acquired heart diseases, central nervous system infections like meningitis/encephalitis, head trauma, sepsis, arrhythmias, sickle cell disease⁶, iron deficiency anemia¹, disorder of coagulation, drug induced,

MATERIAL AND METHODS

It was an observational, prospective, cross-sectional study, conducted at the Neurology department of Childrens Hospital and The Institute of Child Health, Lahore, Pakistan. Children from 1 month to 18 years of age, having focal neurological deficit for >24 hours with radiologically confirmed AIS with 1st ever ischemic stroke were included in the study. Study was conducted during calendar year period November, 2014 - April, 2015 (a total duration of 6 months). Written informed consent

Table-I: Causes of AIS in different age group.

Causes	Age in groups				Total
	Up to 1 year	1-5 years	5-10 years	>10 years	
Iron deficiency	5	15	0	2	22 (30.5%)
Idiopathic	1	10	6	2	19 (26.3%)
Anemia (other causes)	2	15	2	1	20 (27.7%)
CCHD	1	5	0	0	6 (8.3%)
Down syndrome	0	2	3	0	5 (7%)
Total	9	47	11	5	72

Chi-square=3.99, p-value<0.858, Showing the frequencies and association between the causes and different age groups in arterial ischemic stroke in children.

Table-II: Showing statistics of Hb, MCV and serum iron.

Causes	Multiple, Temporal, Occipital areas	Brainstem, basal ganglia, Caudate nucleus, thalamus, Periventricular area	Parietal lobe, Frontal lobe and internal capsule
Anemia	20	0	0
Idiopathic	9	10	0
Iron deficiency anemia	0	9	13
Down syndrome	0	0	5
CCHD	0	0	6
Total	29	19	24

Chi-square=151.20, p-value<0.001.

autoimmune diseases like systemic lupus erythematosus, metabolic diseases (mitochondrial disorders), intracerebral vascular abnormalities (moya moya), Arterio-venous malformation and aneurysms⁷.

Most population based studies on pediatric stroke were from continents other than Asia. There was lack of data of stroke among Asian children. In this study we tried to find out the causes and neuro-imaging findings of children presenting with AIS in a tertiary care center.

was taken from the parents. Study was approved by the institutional review board.

Patients were selected by non-probability convenience sampling technique. Sample size of 72 patients was calculated by using Open Epi sample size calculator, version 3, with 95% confidence level, 5% confidence limit (precision). Percentage of anticipated population (*p*) was 6% ± 5. The sample size was calculated by the following equation

Sample size $n = [DEFF * Np(1-p)] / [(d^2 / Z^2_{1-\alpha/2} * (N-1) + p * (1-p))]$

AIS was confirmed on the basis of history, examination and neuroimaging brain findings. Further investigations were done according to the cause of AIS and CT scan brain findings. The data was collected on proforma. Patients with central nervous system infection, trauma, space occupying lesion and re-current stroke were excluded from the study.

Stroke was defined as sudden onset of a focal neurological deficit due to vascular cause lasting >24 hours. Arterial ischemic stroke is ischemia from blockage of 1 or more arteries supplying brain as detected radiologically by

arteriography, according to history and examination specific labs were done^{2,7}.

Anemia was defined as Hemoglobin (Hb) <10 mg/dl in infants and <8 mg/dl in children, low Mean corpuscular volume is taken as (MCV) <56 in all ages groups. Iron deficiency was taken when S/iron level falls <40 µg/dl in infants and <50 µg/dl in children.

The data was analyzed by using SPSS version 20. Quantitative variables like age was presented as mean and standard deviation while qualitative variables like MRA and MRI findings were presented in frequencies and percentages. Chi-square test (χ^2) was used to compare the variables. A p -value of <0.05 was

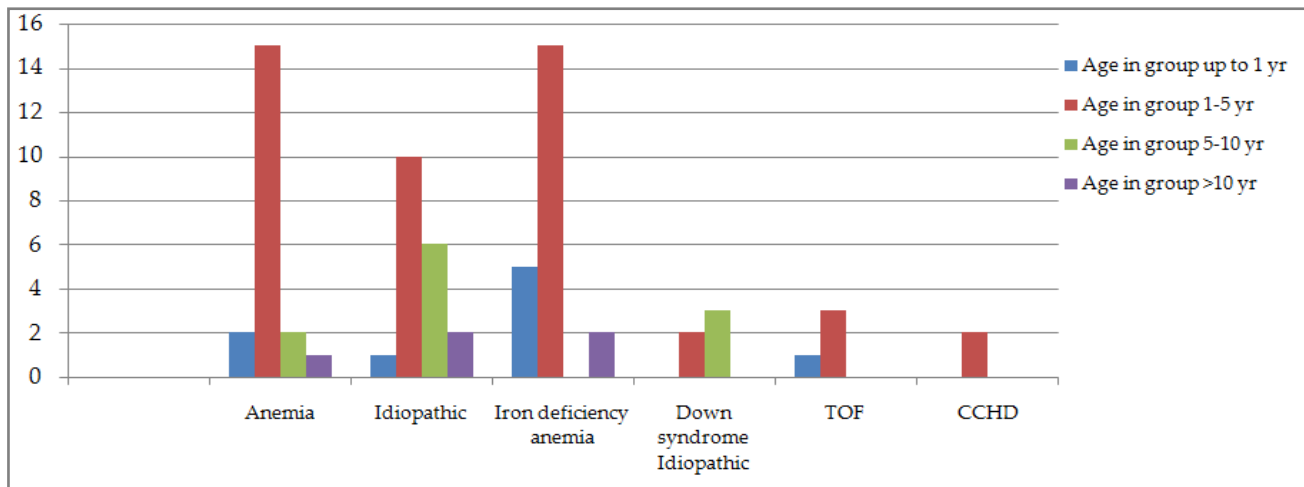


Figure-1: Showing causes of arterial ischemic stroke in different age group.

neuroimaging due to a thrombus or an embolus.

Stroke symptoms include hemiparesis, hemiplegia, slurred speech, aphasia, seizures, worsening or sudden headaches, sudden loss of vision, abnormal eye movements, sudden loss of balance, difficulty in walking, dysphagia, change in mood, cognitive and personality changes^{2,7}. Investigations vary from non-invasive to invasive modalities. In younger children (<18 months of age) cranial ultrasonography was done. Other labs included work up for blood clotting disorder, Electroencephalography, Echocardiography, Computed tomography scan brain, Magnetic resonance imaging, Magnetic resonance

taken as statistically significant.

RESULTS

A total of 72 patients aged from 1 month to 18 years with AIS were identified over a period of 6 months. There was male pre-dominance with male to female ratio of 3:1. Patients were subdivided into 4 age groups. Majority of patients presented between 1-5 years of age followed by school going group between 5-10 years of age (table-I). A p -value was found to be not significant which shows weak relationship between causes and age of children with AIS ($p < 0.858$). Chi-square test (χ^2) was used to compare the variables. A p -value of <0.05 was

taken as statistically significant. The most common mode of presentation of patients was through OPD.

Focal neurological deficit in the form of hemiplegia was the most common presentation in 60 (83%) patients followed by fits in 27 (38%) and hemiparesis in 14 (19%) children. Less common presentations included aphasia, headache, blindness/dysphagia followed by ataxia in 8 (11%), 5 (6.9%), 3 (4.16%) and 1 (1.4%) patient respectively.

Iron deficiency anemia was the most

syndrome who presented with stroke with no heart defects (fig-1).

Table-I & fig-1 show causes of arterial ischemic stroke in different age groups

Children between 1-5 years of age (mean= 44 months) with iron deficiency anemia had lower level of Hb (mean=8.9mg/dl), MCV (mean= 65) and serum iron (mean=64) as compared to other groups (table-II). All patients underwent neuroimaging with equal right to left cerebral hemisphere involvement with ratio of 1:1. MRA was done in 22 cases in which there was

Table-III: Showing the frequencies and association between the causes and radiological findings in arterial ischemic stroke in children.

Statistics				
	Age in months	HB	MCV	IRON
Mean	44.54	8.97	65.63	64.92
Std. Deviation	36.47	2.07	12.84	22.10
Minimum	3.00	4.60	37.00	24
Maximum	180.00	13.70	96.00	115

Table-IV: Comparison of different studies in different regions of the world on spectrum of arterial ischemic stroke in children.

	Our study	Mallick <i>et al.</i> (2008-9) UK	Dowling <i>et al.</i> (2003-7) UK	Maguire <i>et al.</i> (1992-2004) Canada	Chand <i>et al.</i> (2009-15) Pakistan
Mean age	44 months	12 months	67 months	24 months	53 months
M:F	3:1	No gender difference	1.5:1	No gender difference	3:1
Most common Clinical feature	Hemiplegia	Hemiplegia	Hemiplegia	Not seen	Seizure
Most common Cause	Iron deficiency anemia	Not seen	Only cardiac Pts seen	Iron deficiency anemia	Cardiac
Cardiac causes	8.4%	23%	33.3%	excluded	28%
Territorial distribution	MCA→ 57%	Not seen	MCA→67%	Not seen	MCA→56%

frequent cause of stroke in 22 (30.55%) children followed by anemia due to other causes (vitamin B 12 and folic acid deficiency, worm infestation, etc) in 20 children (27.7%) and idiopathic causes in 19 (26.3%) children. Among the congenital heart diseases, 6 (8.3%) patients with cyanotic congenital heart diseases (like tetralogy of fallots and transposition of great arteries with ventricular septal defect) presented with stroke. In this study there were 5 patients with Down’s

suspicion of stroke involving specific arterial territorial involvement as indicated by CT/MRI brain.

The most common single anatomically infarcted area was the parietal lobe in 16 (22%) patients followed by the frontal lobe in 4 (5%) patients. Less commonly, there were few cases who had multiple, temporal and occipital lobe infarctions in 29 (collectively 40%) patients (fig-2). While the deeper structures including basal

ganglia, internal capsule, brain stem, caudate nucleus and thalamus were involved in small number of 19 patients (collectively 26.3%) (fig-2). MRA was done in 22 patients (30.6%). The most commonly involved artery was middle cerebral artery (MCA) in 55% of cases (n=12) followed by internal carotid artery in 14% (n=3) and anterior cerebral artery in 9% (n=2) (fig-3). Data was analyzed and *p*-value was found to be highly significant which shows strong relationship between causes and neuroimaging findings in children with AIS. (*p*<0.001) as shown in (table-III). Chi-square test was used to compare the variables. A *p*-value of <0.05 was taken as statistically significant.

DISCUSSION

Stroke is one of the oldest diseases known to mankind. It was found since the era of Hippocrates and Galen. In 17th century, Thomas Willis found a neonate with fits and the underlying cause was stroke. Therefore, he was the 1st person to provide documented evidence in medical literature⁸. AIS is an important cause of brain insult in children. Few prospective studies in children have been done especially in Asia. Children with AIS aged 1 month to 18 years were studied to evaluate the pattern of causes and radiological findings.

The results of the current study showed male preponderance which is consistent with an international pediatric stroke study⁹. In that study 60% of boys predominated the girls regardless of age, and stroke subtype. That was in contrast to another study done by Mallick *et al* which showed no difference between the two genders⁵.

There was a study done by Mallick *et al* which revealed that younger age, Asian race and black population had increased incidence of stroke⁵. That was parallel to our study in which children between 1-5 years of age were most affected ones.

Presentation of stroke varies with the age. The younger patients present with subtle symptoms like irritability, reluctant to feed,

vomiting and fits. While elder children present with hemiplegia, hemiparesis, headache, fits, visual loss, aphasia, ataxia and cranial nerve palsies¹⁰.

Most of the patients in our study suffered from hemiplegia in 83% (n=60) followed by fits in 38% (n=27) of the patients. The finding of the current study is similar to a study conducted by

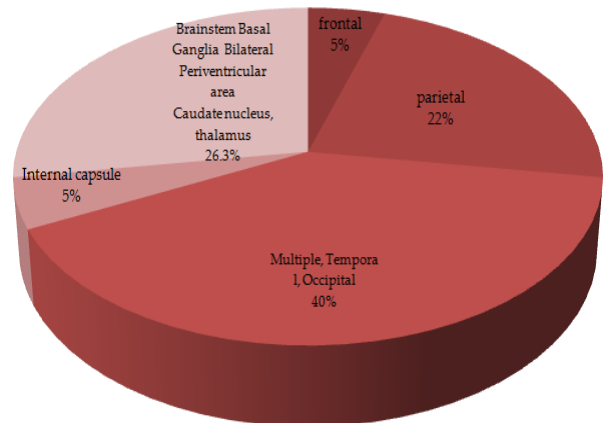


Figure-2: MRI brain findings.

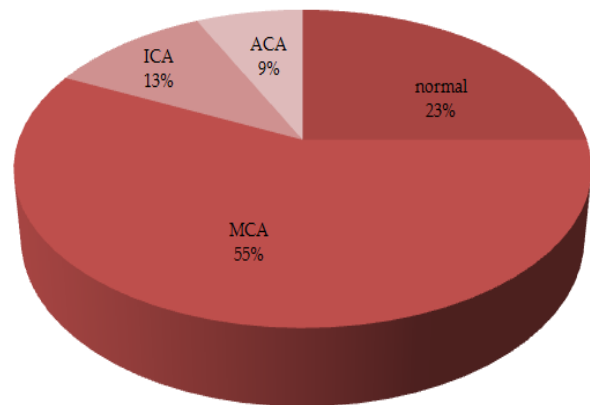


Figure-3: Territorial distribution of stroke n=22 (30%).

Mallick *et al* in which 85% of children presented with focal neurological deficit⁵. In another study carried out by Abend *et al*, 22% of children with AIS presented with fits¹¹.

Iron deficiency anemia has a strong association with AIS in children¹². In the present study 30% of the children had iron deficiency anemia leading to stroke which was similar to a study done by Maquire showing low Hb, MCV and high platelet count¹². Study done by Mackay

et al revealed association of AIS with cardiac causes in 31% of the cases while no risk factor was found in 9% of the patients¹³. In a study conducted by an international pediatric stroke study group cardiac disorders were identified in almost 1/3rd of the children with AIS¹⁴. Both studies were in contrast to our study where 8.4% presented with CHD with AIS. In our study, 25%. Of the children fell under heading of idiopathic etiology of AIS despite of extensive investigations. It is not unusual, in another study done few years back, 17.7% of children had unknown etiology of AIS¹⁵.

A large study was done at a tertiary care hospital in Karachi, over a period of five years but had small number of cases¹⁶, showing male predominance similar to our study. Their age group differed having more cases between 5 to 11 years of children suffering from stroke. Most common presentation was fits (72%) followed by hemiplegia (62%) which was in reverse to the current study. Congenital cyanotic heart diseases also shared more cases (28%) as compared to our patients (8.4%)¹⁶. Another study conducted in 2010 at a tertiary care hospital in Lahore also showed more cases with tetralogy of fallots suffered from cerebrovascular accidents (32%) in contrast to the current study^{17,18}.

The most common single anatomically infarcted area was the parietal lobe in 16 (23%) which comes in MCA territory. The most common involved artery was middle cerebral artery (MCA) in 57% of cases (n=12). These findings are consistent with an another pediatric stroke study revealing the involvement of MCA territory in 67% of patients¹⁴. Similar findings are documented in a study done in Turkey in which MCA was affected in 43% of cases^{18,19}.

The management of acute arterial ischemic stroke in children includes general and specific treatment along with preventive measures, physiotherapy and rehabilitation¹⁹. Outcome includes cerebral palsy, epilepsy, hemiparesis, hemiplegia, aphasia, behaviour, cognitive

impairments and learning disorder²⁰⁻²². Morbidity is 60-70% while death is 6-10%¹.

Our study shows that gender distribution, clinical presentations and territorial distribution on MRA are more or less similar to prior studies. However, differences are in age of presentation as compared to other studies.

The main limitation of this study is small number of patients due to reduced time period. More case-control multicenter studies are needed including good number of patients over a period of years. But this study provides valuable information regarding main causes of AIS in children which can be preventable like iron deficiency anemia.

Key Message

Asia is a continent with developing countries, our children are more at risk of stroke. Neuroimaging has a basic role in diagnosis. Lot of research has to be done by neuro- radiologists, pediatric neurologists and neuro rehabilitation people to help these children.

CONCLUSION

Iron deficiency anemia is one of the common and preventable cause of AIS followed by anemia due to other causes in children. Parietal lobe was found to be the most commonly involved lobe due to infarction of the middle cerebral artery.

CONFLICT OF INTEREST

This study has no conflict of interest to be declared by any author.

REFERENCES

1. Kirton A, Deveber G. Paediatric stroke syndromes. Nelson text book of paediatrics. 19th edition SAUNDERS. Philadelphia: Kliegman RM, MD, Stanton B, MD, Geme J ST et al. 2012: 594 (19th edition); 2080-84.
2. The Johns Hopkins University, the Johns Hopkins hospital and Johns Hopkins health system. All rights reserved Stroke-Pediatric 2014. www.hopkinmedicine.org/neurology_neurosurgery/centersclinics/Pediatricneurology/conditions/stroke_Pediatric.html.
3. Smith SE. Annual incidence rates of arterial ischemic stroke in infants and children range from 0.6 to 7.9 www.uptodate.com/contents/ischemic-stroke-in-children-and-young-adults-etiology-and-clinical-features-of-arterial-ischemic-stroke. This topic last updated: 2014.

4. Johnston SC, Mendis S, Mathers CD. Global variation in stroke burden and mortality: Estimates from monitoring, surveillance and modeling. *Lancet Neurol* 2009; 8(4): 345-54.
 5. Mallick AA, Ganesan V, Kirkham FJ, Fallon P, Hedderly T, McShane T et al. Childhood arterial ischemic stroke incidence, presenting features and risk factors: A prospective population based study. *Lancet Neurol* 2014; 13(1): 35-43.
 6. Lo W, Stephens J, Fernandez S. Paediatric strokes in united states and the impact of risk factors. *Child Neurol* 2009; 24(2): 194-203.
 7. Johnston MV, Coni A. Acute stroke syndromes. 601. Volume 2. 18th ed. Kliegman RM, Behrman RE, Geme J ST, Stanton B; 2008. pp. 2508-12.
 8. Williams AN. Winner of the young physician's section of the Gowers prize 2000. Too good to be true? Thomas Willis-neonatal convulsions, childhood stroke and infanticide in seventeenth century England. *Seizures* 2001; 10(7): 471-83.
 9. Golomb MR, Fullerton HJ, Nowak-Gotti U, Deveber G. International pediatric stroke study group [Make pre-dominance in childhood ischemic stroke: Findings from the IPSS.] *Stroke* 2009; 40(1): 52-7.
 10. Delsing BJ, Catsman-Berrevoets CE, Appel IM. Early prognostic indicators of outcome in ischemic childhood stroke. *Pediatric Neurol* 2001; 24(4): 283-9.
 11. Abend N, Beslow LA, Smith SE, Kessler SK, Vossough A, Mason S, et al. Seizures as a presenting symptom of AIS in childhood. *J Pediatr* 2011; 159(3): 479-83.
 12. Maquire JL, Deveber G, Pankin PC. Association between Iron deficiency anemia and stroke in young children. *Pediatrics* 2007; 120(5): 1053-7.
 13. Mackay MT, Wiznitzer M, Benedict SL, Lee KJ, Deveber GA. Arterial ischemic stroke risk factors: The international pediatric stroke study. *Ann Neurol* 2011; 69(1): 130-40.
 14. Dowling MM, Hynan LS, Lo W, McClure C, Yaqer JY, Dlamini N. International paediatric Stroke study group. *Int J stroke* 2013; 8 (Suppl A-100): 39-44.
 15. Siddiqi 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(2): 60-3.
 16. Chand P, Ibrahim S, Matloob A, Arain F, Khealani B. Acute childhood ischemic stroke; A Pakistani tertiary care hospital experience. *Pak J Neurol Sci* 2016; 11(1): 3-6.
 17. Aftab S, Usman A, Sultan T. Frequency of cerebrovascular accidents and brain abscess in children with tetralogy of fallots. *Pak J Neurol Sci* 2015; 10(2): 23-6.
 18. Yimencioğlu S, Yakut A, Ekici A, Carman KB, Kocak O et al. Evaluation of pediatric stroke patients. *J Clin Case Rep* 2015; 5(12): 1-4.
 19. Pappachan J, Kirkham FJ, Pappachan J, Kirkham FJ. Cerebrovascular disease and stroke. *Arch Dis Child* 2008; 93(10): 890-8.
 20. Ganesan V, Hogan A, Shack N, Gordon A, Isaacs E, Kirkham FJ. Outcome after ischemic stroke in childhood [PubMed]. *Dev Med Child Neurol* 2000; 42(7): 455-61.
 21. Steinlin M, Roellin K, Schroth G. Long-term follow-up after stroke in childhood. *Eur J Pediatr* 2004; 163(4-5): 245-50.
 22. Lee JC, Lin KL, Wang HS, Chou ML, Hung PC, Hsieh MY et al. Seizures in childhood ischemic stroke in Taiwan. *Brain Dev* 2009; 31(4): 294-9.
-