Stroke in Saudi children

Epidemiology, clinical features and risk factors

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ABSTRACT

Objectives: To describe the epidemiology and clinical features of stroke in a prospective and retrospective cohort of Saudi children and ascertain the causes, pathogenesis, and risk factors.

Methods: The Retrospective Study Group (RSG) included children with stroke who were evaluated at the Division of Pediatric Neurology, or admitted to King Khalid University Hospital, College of Medicine, King Saud University, Riyadh, Kingdom of Saudi Arabia during the period July 1992 to February 2001. The Prospective Study Group (PSG) included those seen between February 2001 and March 2003.

Results: During the combined study periods of 10 years and 7 months, 117 children (61 males and 56 females, aged one month-12 years) were evaluated; the majority (89%) of these were Saudis. The calculated annual hospital frequency rate of stroke was 27.1/100,000 of the pediatric (1 month – 12 years) population. The mean age at onset of the initial stroke in the 104 Saudi children was 27.1 months (SD = 39.3 months) and median was 6 months. Ischemic strokes accounted for the majority of cases (76%). Large-vessel infarcts (LVI, 51.9%) were more common than small-vessel lacunar lesions (SVLL, 19.2%). Five patients (4.8%) had combined LVI and SVLL. Intracranial hemorrhage was less common (18.2%), whereas sinovenous thrombosis was diagnosed in 6 (5.8%) patients. A major risk factor was identified in 94 of 104 (89.4%) Saudi children. Significantly more hematologic disorders and coagulopathies were identified in the PSG compared to the RSG (p=0.001), reflecting a better yield following introduction of more comprehensive hematologic and coagulation laboratory tests during the prospective study period. Hematologic disorders were the most common risk factor (46.2%), presumed perinatal ischemic cerebral injury was a risk factor in 23 children (22.1%) and infectious and inflammatory disorders of the circulatory system in 18 (17.3%). Congenital and genetic cerebrovascular anomalies were the underlying cause in 7 patients (6.7%) and cardiac diseases in 6 (5.8%). Six patients (5.8%) had moyamoya syndrome, which was associated with another disease in all of them. Inherited metabolic disorders (3.8%) included 3 children with Leigh syndrome and a 29-month-old girl with mitochondrial encephalomyopathy, lactic acidosis, and stroke-like episodes. Systemic vascular disease was a risk factor in 3 children (2.9%) including 2 who had hypernatremic dehydration; and post-traumatic arterial dissection was causative in 3 cases (2.9%). Several patients had multiple risk factors, whereas no risk factor could be identified in 11 (10.6%).

Conclusion: Due to the high prevalence and importance of multiple risk factors, a comprehensive investigation, including hematologic, neuroimaging and metabolic studies should be considered in every child with stroke.

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Although the plasticity of the developing brain is thought to be among the reasons for better functional recovery after stroke in children, yet it has been established that 62-100% of children surviving a stroke develop some residual deficit.[1-7] The magnitude of the resulting economic, social, and psychological impact can easily be realized given that affected children have many disabled years ahead of them. The neurologic sequelae of childhood stroke include motor deficits, seizures, mental retardation, learning disability, and speech abnormalities.[7,8] Cerebrovascular disorders are within the top 10 causes of death in children.[9] During the past 10 years, the reported incidence of childhood ischemic stroke has increased to 2-6/100,000 children/year, reflecting increased detection related to clinical awareness and neuroimaging techniques.[10] This also reflects the increased number of children who now survive previously lethal disorders associated with stroke, such as leukemia and congenital heart disease.[10,11] However, research on pediatric stroke is still at its infancy and baseline epidemiological data are scarse.[10] The identification of causes and risk factors of stroke in children in a given population is important since many of these are age and population specific. It is well-known that atherosclerosis is not a common etiology of stroke in young patients.[12] When present, conditions causing early and accelerated atherosclerosis, such as inherited and familial lipid disorders, need to be considered,[13-15] since early management may reduce further cerebrovascular and cardiovascular morbidity. Non-atherosclerotic risk factors also have different features in children compared to adults and vary in their prevalence from one population to another. Studies on stroke in Saudi Arabia have dealt mainly with adult populations.[16-26] Hence, the identification of risk factors was geared to causes known to be associated with atherosclerosis (for example, hypertension and diabetes mellitus), leaving the predisposing factors to childhood stroke under represented. Three studies dealt with stroke in children. The first of these described the clinical and brain CT features of old infantile hemiplegia in 48 patients seen at King Khalid University Hospital (KKUH) in Riyadh.[27] The age group in this study ranged from 1-45 years (median 23 years). The study highlighted the importance of tuberculosis as a causative factor. The second study[28] described 21 cases of stroke (aged between 4 months and 15 years) that were seen in 2 large hospitals in Riyadh and Al-Khobar of the Eastern Province. The third study[29] reported on 31 children who were seen at the same hospital in Al-Khobar. Underlying sickle cell disease (SCD) or trait accounted for one incidence of stroke (5%) in the second study[28] and 2 (6%) in the third,[29] reflecting the mild spectrum of SCD in the Eastern Province. In these 3 studies, investigations to reveal the impact of Mendelian inheritance on stroke risk factors were not explored. In particular, inherited coagulation defects (for example, protein C, S and antithrombin III) and neurometabolic causes (for example, homocystinuria, branched chain amino acidopathies) were not looked for. The contribution of mitochondrial diseases was also not assessed in the first 2 studies.[27,28] The current study describes the epidemiology and clinical features of stroke in a retrospective and prospective cohort of Saudi children and outlines similarities with, and differences from, similar studies in developing and developed countries. It also ascertains the causes and risk factors of stroke in this cohort.

Definition of stroke. In the old pediatric literature, the term "stroke" has not been clearly defined as in adults. Prior to the use of CT, clinical studies referred to "acute hemiplegia of childhood."[2,29,30] The later term includes non-vascular causes of childhood hemiplegia and excludes infarctions without motor deficit. In the present study, the term "stroke" will refer to symptomatic hemorrhagic or ischemic injury to the brain with a distribution consistent with a vascular etiology.[8,31] The symptoms and signs of stroke must last for at least 24 hours and the hemorrhage or ischemia must be the primary cause of the brain injury. The use of this definition will exclude not only transient causes of hemiparesis (for example, Todd's paralysis) but also other causative factors with similar presentation; for example, diffuse traumatic brain injury, global cerebral ischemia, bleeding into a tumor, and focal infections such as herpes simplex encephalitis. It will also exclude the syndrome of hemiconvulsion-hemiplegia-epilepsy (HHE), which results from evolving edematous swelling of one hemisphere, following prolonged status hemiconvulsions.[32]

Methods. The study included children with suspected cerebrovascular disease, who were evaluated at the Division of Pediatric Neurology (DPN) or were inpatients in the Pediatric Wards at KKUH, Riyadh, Kingdom of Saudi Arabia. These patients were recruited from those who presented with weakness of one or more extremities, sudden onset of consciousness impairment, suspected meningitis/encephalitis, recurrent headaches, and focal or generalized seizures. As stipulated in its design, the study covered 10 years and 7 months and has 2 components as follows:

Retrospective study. All the case records of children who were evaluated at the DPN, or admitted

to KKUH with the clinical diagnosis of stroke during the period from July 1992 to February 2001 were reviewed. Patients who fulfilled the clinical diagnosis of stroke, as defined above, and confirmed by brain CT, MRI, or both were included. As facilities were unavailable at KKUH, MRI arrangements for the pediatric neurology patients were made at King Fahad National Guard Hospital from 1993 to 1999. Relevant information about each child was retrieved. This included age at onset of stroke, sex, nationality, history of associated disorders or known risk factors (for example, cardiac, hematological and infectious diseases), consanguinity of parents and any family history of similar conditions. Various treatments received, sequelae and outcome were also recorded for each child. It has been the policy of the DPN to perform a battery of investigations for all cases of stroke as detailed in **Table 1**. These were used to differentiate between cerebral infarction and hemorrhage and for the establishment of a possible etiological cause, on the bases of the cumulative clinical data and salient investigations. A comprehensive form for retrospective patient clinical, and laboratory data retrieval was designed and completed for each patient.

Prospective study. This included all patients seen between February 2001 and March 2003. Data retrieval was similar to that used in the retrospective study. Investigations for these cases are also shown in **Table 1**. Cerebral and aortic digital subtraction angiography was confined to selected cases when a vascular anomaly was suspected (for example, moya-moya disease, aneurysm, arteriovenous malformation and arterial dissection). During this prospective period, the facility for MRI and magnetic resonance angiography (MRA) became available for patients at KKUH following the start of the MRI service in May 1999. Screening for children with SCD by transcranial Doppler studies (using DWL, Multi Dop X4, Germany) became available during the last 4 months of the prospective study, through collaboration with the Neurosciences Department, Riyadh Al-Kharj Hospital (RKH) Program, Riyadh, Kingdom of Saudi Arabia. During the same latter period, children with

Table 1 - Investigations of stroke in a child.

Imaging	***Chest and cardiovascular system***
Cranial computed tomography (CT)	Chest x-ray
Magnetic resonance imaging (MRI)	Electrocardiogram (ECG)
Magnetic resonance angiography (MRA)	Transthoracic echocardiogram
Magnetic resonance venography (MRV)	Transesophageal echocardiogram*
Cerebral and aortic digital subtraction angiography*	
Cranial ultrasound*	***Investigations for infectious, inflammatory, and other metabolic risk factors***
Cervical spine x-ray or CT*	Blood cultures*
Single photon emission computed tomography (SPECT)*	Cerebrospinal fluid examination*
Transcranial Doppler*	TORCHS screening*
Duplex scan*	Antinuclear antibodies (ANA)
	Anticardiolipin antibodies (ACLA)
Hematologic	Serum brucella titre
Complete blood count (CBC) including platelets	Mycoplasma IgM antibodies*
Erythrocyte sedimentation rate (ESR)	Syphilis serology, HIV titre, TB skin testing*
Sickling test	Fasting glucose*
Bleeding time	Serum lactate*
Prothrombin time (PT)	Serum pyruvate*
Activated partial thromboplastin time (APTT)	Serum ammonia*
Reptilase time (RT)*	Blood amino acids
Plasma fibrinogen	Lipid profile*
Thrombin – antithrombin complex (TAT)*	Anion gap estimation*
Fibrinopeptidase A (FPA)*	Serum lysosomal enzymes*
Prothrombin fraction 1 + 2 (F1 + 2)*	
Plasminogen activator inhibitor (PAI)*	***Muscle biopsy****
Protein C (functional and antigenic assays)	Histology and histochemistry
Protein S	Electron microscopy
Antithrombin III (functional and antigenic assays)	Mitochondrial enzyme assay
Activated protein C resistance assay*	Mitochondrial DNA analysis
Clotting factors assays (Factors VII, VIII, IX, X, XI, XIII)*	
Platelet function test*	***Neurophysiological tests****
Hemoglobin electrophoresis*	Routine EEG
	Video EEG
	Visual evoked potentials (VEP)
Urinalysis	Electroretinogram (ERG)
Urine for neurometabolic screening	Brain auditory evoked potentials (BAEP)
Urinary organic acids	
	Other miscellaneous tests*
	Karyotype
	Skin fibroblast culture
*Indicates studies that are appropriate in selected cases	

suspected cerebrovascular disease involving the neck muscles (for example, SCD and arterial dissection) were also evaluated with a Duplex scan (using HDI 5000 ALT, USA) at the Vascular Laboratory, Division of Vascular Surgery, KKUH.

Laboratory studies. Most of the hemostatic assays were well established in the Coagulation Laboratory, Physiology Department, College of Medicine, Riyadh, Kingdom of Saudi Arabia, while others were started during the prospective study period. The details of these are to be found elsewhere.[33] Investigations for cases suspected to have mitochondrial encephalomyopathy, for example, mitochondrial encephalomyopathy with lactic acidosis and stroke-like episodes [MELAS] and Leigh syndrome needed special arrangements and are also detailed elsewhere.[34]

Statistical analysis. The Stat Pac Gold statistical analysis package was used for data management. Paired t-test (two-tailed) and Fisher's exact test were used for comparison of data among the different groups. A probability value of $p<0.05$ was considered to be significant.

Results. During the study period of 10 years and 7 months, 171 children (aged one month to 12 years) with clinical diagnosis of stroke were admitted to KKUH or seen at the Pediatric Neurology Clinics. Of these, 54 were excluded from the study since they did not conform with the definition of stroke as stipulated earlier. This latter group consisted of 32 children who had traumatic brain injury (30 due to accidents and 2 were non-accidental), and 10 children with focal infection due to herpes simplex encephalitis, 6 with HHE syndrome, 4 who had bleeding into a tumor, and 2 who proved to have had Todd's paralysis. The remaining 117 children, who were included in the study consisted of 61 males and 56 females (male: female ratio = 1.1:1). Six (5.1%) were <1 year, 16 (13.7%) were aged 1-7 years and the rest (81.2%) were older. The majority of these children (n = 104; 88.9%) were Saudis. During the retrospective study period, extending for 8 years and 7 months, 91 stroke children were seen, whereas the prospective study group (PSG) consisted of 26 children who were seen over 2 years. The total number of children who were seen at the Pediatric Neurology Clinics or admitted at KKUH during this period was 40,786. Given the 117 stroke children who were included in the study, the calculated annual hospital frequency rate would be 27.1/100,000 of the pediatric (one month to 12 years) population.

Clinical features and types of stroke in Saudi children. When first seen, the mean age of the 104 Saudi children was 55 months (SD ± 41.7) and median was 48 months. The duration of period from the onset of the initial stroke to evaluation at KKUH, ranged from <1-155 months (mean ± SD: 27 ± 34.8 months; and median: 11 months). Twenty-five patients (24%) were seen at KKUH within one month from the onset of the initial stroke, whereas 46 (44.2%) were evaluated within 6 months. The mean age at onset of the initial stroke was 27.1 months, and median was 6 months (**Table 2**), and was similar in boys and girls. The majority of children had their stroke in infancy (<12 months), whereas 14.4% were older than 7 years. History of parental consanguinity was established in 43 (41.3%) cases and history of other family members who had a stroke in 11 (10.6%). There was no significant association between parental consanguinity and family history of stroke (p=0.2). The initial symptoms, signs and types of stroke are shown in **Table 3**. Unilateral or bilateral weakness (motor deficit) was the most common presenting symptom. More than half of the children presented with symptoms suggestive of increased intracranial pressure. Thirty-eight presented with irritability and 25 had headache, or vomiting, or both. Seizures were also common. Two children had infantile spasms, and EEG examination of one revealed hemi-hypsarrhythmia (**Figure 1**). Isolated or combined cranial nerve palsies were also common, whereas aphasia, coma and macrocephaly occurred less frequently. Arterial ischemic strokes (affecting 79 out of 104 children [76%]) accounted for the majority of cases. Of the ischemic strokes, large-vessel infarcts were more common than small-vessel lacunar lesions. Five patients had combined large-vessel arterial ischemic and lacunar infarcts. Intracerebral hemorrhage was less common, whereas, sinovenous thrombosis was diagnosed in 6 patients.

Risk factors for stroke in Saudi children. One major risk factor was identified in 93 of 104 (89.4%) Saudi children (**Table 4**). Of the 81 children in the retrospective study group (RSG), no risk factor was found in 11, whereas one or more risk factors could be identified in all of the 23 children in the PSG. In this respect, the difference between the 2 groups was highly significant (p=0.0006). Comparisons between the proportions of identified risk factors in the prospective and retrospective study groups showed significant differences in the identification of hematologic disorders and coagulopathies. The proportion of children in the PSG (18 of 23, or 78.3%) was significantly higher compared to the 30 of 81 (37%) with identified hematologic risk factor(s) in the RSG (p=0.001). There was no significant difference between the prospective and retrospective study groups in the frequency of the other risk factors.

Table 2 - Gender and age at onset of initial stroke of 104 Saudi children.

Age (months)	Males	Females	Total	(%)
< 12	34	29	63	(60.6)
12 – 48	9	8	17	(16.3)
49 - 84	7	2	9	(8.7)
85 -	6	9	15	(14.4)
Total	**56**	**48**	**104**	**(100)**
Percent	54	46	100	
Mean	27.1	27.2		
Standard Deviation	37.6	41.6		
Median	6	6		

Table 3 - Initial presenting symptoms, signs, and types of stroke in 104 Saudi children.

Symptoms, signs and types	Cases	(%)
1. Presenting symptoms and signs		
Weakness (motor deficit)	92	(88.5)
Hemiparesis/hemiplegia:	70	(67.3)
Right	40	
Left	30	
Bilateral motor deficit	22	(21.2)
Symptoms suggestive of increased intracranial pressure		
Irritability	38	(36.5)
Vomiting	14	(13.5)
Headache	11	(10.6)
Seizures:	49	(47.1)
Generalized	27	
Focal	20	
Infantile spasm (myoclonic)	2	
Cranial nerve palsy (isolated or combined)	35	(33.7)
Aphasia	22	(21.2)
Coma	17	(16.3)
Macrocephaly	5	(4.8)
2. Type of stroke		
Large-vessel arterial ischemic	59*	(56.7)
Lacunar infarct	25*	(24)
Intracranial hemorrhage	19	(18.2)
Sinovenous thrombosis	6	(5.8)

*5 patients had combined arterial ischemic and lacunar infarcts

Table 4 - Risk factors for stroke in 104 Saudi children.

Risk factor*	Cases	(%)
Prothrombotic and coagulation disorders	**48**	**(46.2)**
Prothrombic disorders	33	(31.7)
Sickle cell disease	12	(11.5)
Coagulation factor deficiency	3	(2.9)
Hypochromic microcytic anemia	27	(26)
Presumed perinatal ischemic cerebral injury	**23**	**(22.1)**
Infectious and inflammatory disorders of the circulatory system	**18**	**(17.3)**
Infectious disorders	**16**	**(15.3)**
Acute purulent meningitis	5	(5.8)
Meningitis/meningoencephalitis (unspecified)	4	(3.8)
Congenital infections	3	(2.9)
Septicemia	2	(1.9)
Neurobrucellosis	2	(1.9)
Inflammatory diseases: Systemic lupus erythematosus	**2**	**(1.9)**
Congenital and genetic cerebrovascular anomalies	**7**	**(6.7)**
Sturge-Weber syndrome / Klippel-Trenaunay syndrome	3	(2.9)
Neurofibromatosis type 1	1	(1)
Polycystic kidney-autosomal dominant with aneurysm	1	(1)
Intracranial aneurysm	1	(1)
Arteriovenous malformation	1	(1)
Cardiac diseases	**6**	**(5.8)**
Congenital heart disease	5	(4.8)
Acquired heart disease	1	(1)
Vasculopathies: Moyamoya syndrome	**6**	**(5.8)**
Inherited metabolic disorders	**4**	**(3.8)**
Leigh syndrome	3	(2.9)
Mitochondrial encephalomyopathy, lactic acidosis, and stroke-like episodes (MELAS)	1	(1)
Systemic vascular disease	**3**	**(2.9)**
Hypernatremic dehydration	2	(1.9)
Systemic hypotension	1	(1)
Post-traumatic arterial dissection	**3**	**(2.9)**
No risk factor found	**11**	**(10.6)**

Totals in bold, *Some patients had more than one risk factor

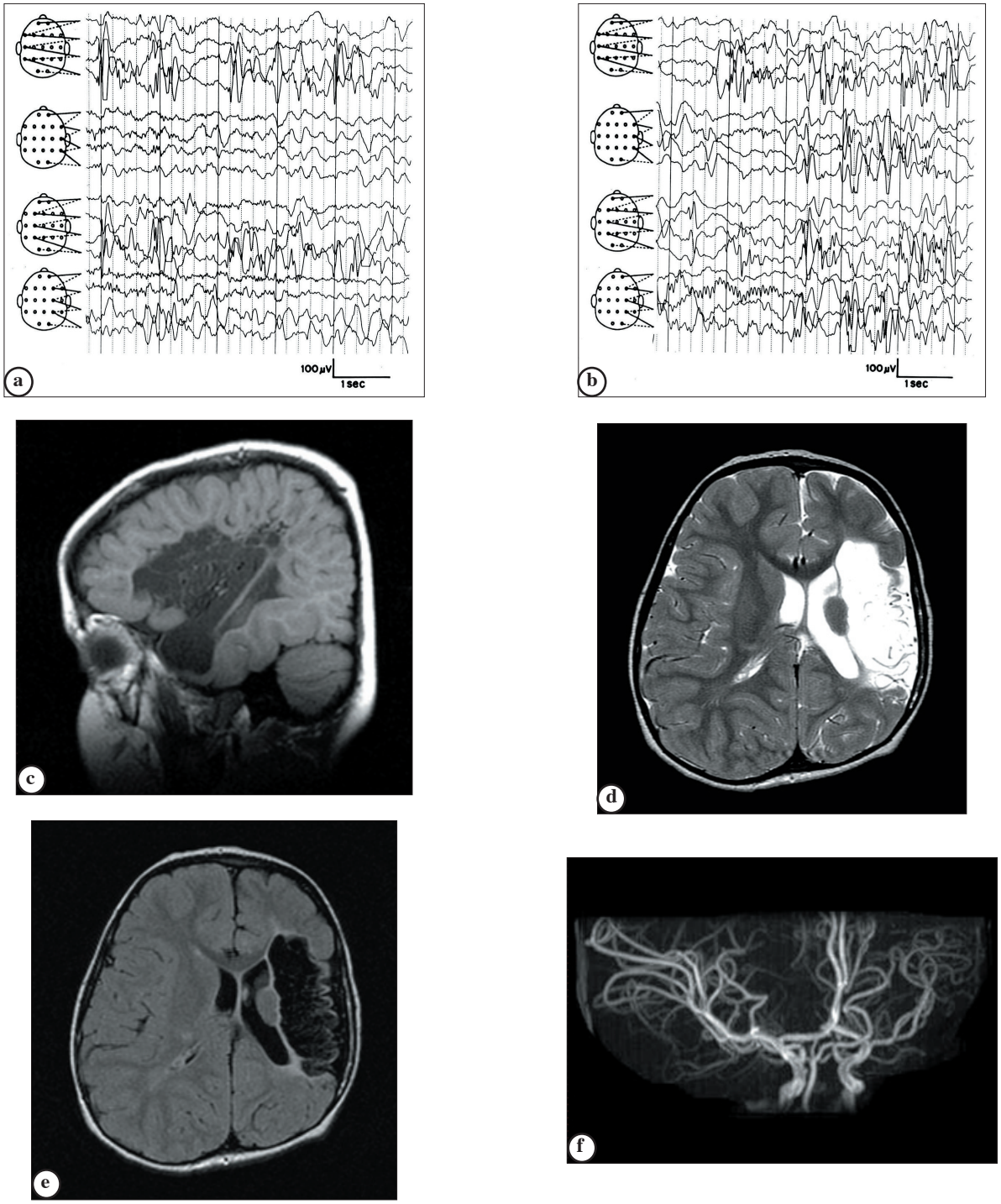

Figure 1 - Sleep/sedated EEG of a 6-month-old boy with infantile spasm and left cerebral infarction. **a)** The background is asymmetric with hemihypsarrhythmia (high voltage slow waves, irregularly mixed with spikes and sharp waves that occur randomly) involving the left hemisphere. **b)** There is a burst of sharp waves seen bilaterally, followed by electro decrement associated with fast activity in the right anterior-to-midtemporal regions (sign of development of tonic spasm). This is followed by generalized hypsarrhythmic pattern. **c)** Sagittal T1-weighted brain MR image, **d)** axial T2-weighted image and **e)** Axial FLAIR image showing small left cerebral hemisphere with left temporo-frontal encephalomalacia due to old infarction along the territory of the left middle cerebral artery. **f)** Magnetic resonance angiography showing small caliber and reduced number of branches of the left middle cerebral artery.

Discussion. Once thought to be rare, stroke is becoming increasingly recognized.[9,10] Research, as well as publications on childhood stroke, only recently started to provide the scientific basis for management strategies.[8,10] These included the publication of single and multicenter cohort studies and evidence-based guidelines originating from multicenter networks of investigators.[3,10] The present study included 117 children who were seen during a period of 10.6 years in one institute, thus forming one of the largest groups of children with stroke studied at one centre worldwide. For comparison, the Stroke Registry of Dijon, Service of Neurology, France, ascertained during 9 full calendar years 28 stroke patients from a population of 23,877 resident children.[35] Another study[28] from Saudi Arabia involved 21 cases of stroke observed in children (age 4 months to 15 years) who attended 2 large hospitals in Riyadh and Al-Khobar (of the Eastern Province) over a 10-year-period (1982-1992). A subsequent study[29] undertaken in the same hospital in Al-Khobar reported 31 Saudi children with stroke over a 5-year period (July 1991-June 1996). The reason for this relatively large number of patients in the present study reflects the functional nature of KKUH in Riyadh, which provides both secondary and tertiary care, as well as services for Riyadh and other regions of Saudi Arabia. The present cohort is comparable to the number of 212 children with arterial ischemic stroke, seen over 22 years in a single tertiary centre in London.[36] The reported incidence of childhood stroke is approximately 2.5 to 3.1 cases per 100,000 children per year,[37] but has risen during the last 2 decades and is now exceeding 8 per 100,000 children per year.[38,39] The reason for this apparent increased incidence is the recent availability of increasingly sensitive and specific methods of non-invasive neuroimaging techniques, including cranial ultrasound studies, CT, MRI and MRA.[39] In the present study, the calculated annual stroke hospital frequency rate is comparable to the incidence of 29.7 per 100,000 children reported in a similar hospital-based study from the Eastern Province.[29]

Clinical features and types of stroke in Saudi children. Analysis of the clinical features of stroke in the Saudi children who were seen during the study period (**Table 2**) revealed a mean age of onset of <3 years with the majority of children acquiring the disease in infancy (<12 months); and a minority had stroke when they were older than 7 years. This is quite similar to the findings of the study on 31 children from the Eastern Province,[29] whose corresponding figures were 26.2 months (mean), 58% (age <12 months) and 16% (age > 7 years). Parental consanguinity was remarkable in this cohort, confirming the high prevalence observed in previous studies.[40-43] However, the association between parental consanguinity and family history of stroke did not attain significance. In 104 Saudi patients, stroke presented with hemiparesis/hemiplegia in 67.3%, seizures in 47.1% and aphasia in 21.2%. In the Canadian Pediatric Ischemic Stroke Registry (CPISR),[3] one of the largest cohort of stroke in children, arterial ischemic stroke had similar presentations; hemiparesis was observed in 51%, seizures in 48% and speech disorders in 17%. Although focal neurological deficits can be detected initially, on careful neurological examination, seizures and decreased level of consciousness are common presentations of stroke in young children, particularly those <4 years of age.[44] It is noteworthy that 2 of the infants in the present study had infantile spasm at presentation which was associated with hemi-hypsarrhythmia on EEG, in one infant (**Figure 1**). Infantile spasms due to unilateral cerebral infarcts have been described before.[45] In later childhood, stroke may manifest as hemiplegia, altered level of consciousness, aphasia, or as other focal neurological disturbance.[46] Ischemic strokes accounted for the majority of cases in the present study, and afflicted patients with large-vessel arterial ischemic lesion (LVAIL),[20] lacunar infarcts, sinovenous thrombosis, and combined LVAIL and lacunar infarcts. Hemorrhagic stroke accounted for only 18.2% of cases. This is similar to the findings in one of the studies[29] from the Eastern Province, where ischemic strokes were observed in 90% and hemorrhagic strokes in 10% of 31 children. An earlier study[29] from the Eastern Province on 21 children reported a higher proportion of cerebral hemorrhage (43%). Sinovenous thrombosis was not reported in either of the 2 previous studies, since in both, MRV was not available as a neuroimaging tool.[28,29] In a recent epidemiological study[24] on stroke in 71 adults from the Western Region, the type of stroke in Saudis was ischemic in 77% and hemorrhagic in 20.5%. The proportion of ischemic stroke in the present study is higher than that observed worldwide. In the US National Hospital Discharge Survey from 1980 through 1998,[38] in children 0-18 years, ischemic stroke was reported in 7.8/100,000, and hemorrhagic stroke in 2.9/100,000 children per year. The relative paucity in the proportion of hemorrhagic stroke in the present cohort compared to other studies,[47] may be partly accounted for by exclusion, in this study, of cases with intraparenchymal bleeding due to brain tumors and cases of herpes encephalitis. It is also possible that children with hemorrhagic stroke, especially those due to hereditary bleeding disorders, succumb before they manage to reach the secondary or tertiary care hospitals. It has also been observed

that most of those patients came from rural areas and often made long journeys to come for treatment.[48]

In the present study, a major risk factor for stroke was identified in 89% of cases. Significantly higher proportion of children in the PSG had an identifiable risk factor, compared to the RSG. This was apparent with regards to the identified hematologic disorders and coagulopathies, emphasizing the importance of availability of equipped coagulation laboratory in the investigation of childhood stroke. Hematologic disorders were the most common risk factor.[33] Contrary to the observations in previous similar studies from Saudi Arabia,[28,29] SCD accounted for a significant proportion of the confirmed risk factors. These SCD patients also had severe manifestations, highlighting the severe phenotype of SCD which is also prevalent in Saudi Arabia in addition to the mild form.[33] Presumed perinatal ischemic cerebral injury was a risk factor in approximately one quarter of cases,[49] followed by infectious and inflammatory disorders of the circulatory system.[50] The latter group included the first reported cases of childhood stroke following neurobrucellosis.[50] Congenital and genetic cerebrovascular anomalies were the underlying cause in 7 patients and cardiac diseases in 6.[51,52] Six patients had moyamoya syndrome (MMS), associated with another disease in 5 of them.[53] The association of MMS and protein C deficiency was first reported in this cohort of patients.[53] On the other hand, the association with another 2 dermatologic syndromes, namely wrinkly skin syndrome (OMIM 278250) and Adams-Oliver syndrome (OMIM 100300), has not, hitherto, been described.[53] Inherited metabolic disorders (3.8%) were noted in 3 children with Leigh syndrome and a 29-month-old girl with MELAS.[34] Systemic vascular disease was a risk factor in 3 children, including 2 who had hypernatremic dehydration;[54] and post-traumatic arterial dissection was causative in 3 cases.[55] Several patients had multiple risk factors.

The present study strongly highlighted the importance of prothrombotic disorders as a risk factor for stroke in Saudi children.[33] Because of the high prevalence and importance of multiple risk factors, a comprehensive investigation, including hematologic, neuroimaging and metabolic studies should be considered in every child with stroke.

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