Hematologic risk factors for stroke in Saudi children

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ABSTRACT

Objective: To explore the hematologic risk factors for stroke in a cohort of Saudi children.

Methods: We evaluated children at the Division of Pediatric Neurology at King Khalid University Hospital, College of Medicine, King Saud University, Riyadh, during the periods July 1992 to February 2001 (retrospective study) and February 2001 to March 2003 (prospective study). Investigations for suspected cases included neuroimaging, transcranial Doppler (TCD) for cases of sickle cell disease (SCD), and Duplex scan. Hemostatic assays included coagulation screening tests, tests of thrombin generation and fibrinolysis, coagulation inhibitors, and activated protein C resistance.

Results: During the study period, 104 Saudi children (aged one month to 12 years) with stroke were seen. The mean age of the cohort was 27.1 months (SD = 39.3 months) and median was 6 months. Ischemic strokes accounted for the majority of cases (76%). A major risk factor was identified in 93 of 104 cases of stroke (89.4%). Hematologic disorders were the most common (46.2%), followed by prothrombic disorders (31.7%); microcytic hypochromic anemia (26%); sickle cell disease (SCD), or SCß°-thalassemia, (11.5%), and factor IX deficiency (2.9%). Raised anticardiolipin antibodies (13/49, 26.5%) was the most frequent abnormality. Deficiencies of the natural anticoagulants (protein S, protein C and antithrombin III) were as follows: protein S (15/70, 21.4%); protein C (15/70, 21.4%) and combined deficiency of 2 or more inhibitors (9/70, 12.9%). Activated protein C resistance has not been detected. Contrary to the findings of previous studies from Saudi Arabia, SCD is a common risk factor and is severe, as it resulted in multiple strokes. Moyamoya syndrome was diagnosed in 2 patients with SCD, one of whom had revascularization surgery (encephaloduroarterio-synangiosis). Assessment of children with SCD at risk of stroke was helped by the introduction of TCD followed by neuroimaging, using MRI and magnetic resonance angiography.

Conclusions: The study strongly highlights the importance of prothrombotic disorders and the severe phenotype of SCD as risk factors for stroke in Saudi children.

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A variety of hematologic disorders can cause stroke in children, secondary to intracranial hemorrhage or thrombosis. Of these, sickle cell disease (SCD) stands out as an important risk factor in populations where its gene is prevalent.[1] Nearly 10% of patients with SCD develop a stroke, and approximately half of these will have a recurrence.[2] Most of the strokes occur before the age of 10 years.[3] Sickle cell disease is common in Saudi Arabia and presents with a spectrum of clinical diversity.[4] In most cases, strokes

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are the result of large-vessel occlusive disease, involving the distal intracranial segment of the internal carotid artery (ICA), and proximal anterior and middle cerebral arteries (MCA).[5-7] Progressive development of lenticulostriate collateral vessels after occlusion of these large vessels results in moyamoya syndrome (MMS). The development of moyamoya (Japanese for "hazy puff of smoke" which describes an angiographic pattern) significantly increases the risk of recurrent cerebrovascular events including stroke and transient ischemic attacks.[8] The disease has also been associated with both intraparenchymal and subarachnoid hemorrhage.[9] Hemorrhage occurs as an isolated event in younger patients or around the time of sickle crisis.[10] In contrast, older patients with SCD have a greater risk than children of an aneurysm or arteriovenous malformation.[11] Endothelial injury, probably caused by the abnormal erythrocytes, and the presence of generalized elastic tissue defect and fragmentation of the internal elastic lamina of the arterial walls, have also been reported.[12,13] Other factors operating in the pathogenesis of stroke in SCD, are vascular tone instability and vulnerability to fluctuations in nitric oxide levels and a decrease in cerebral reserve capacity.[1] Recently, transcranial Doppler (TCD) contributed significantly to the management of patients with SCD. It proved to be valuable in detecting arterial stenosis with velocities of 200 cm/sec or higher being associated with a high risk of cerebral infarction.[14-16] Placement of children with SCD, who had abnormal results on TCD, in a transfusion program resulted in a drastic reduction in the risk of a first stroke.[17] Reduction of the risk for stroke recurrence to as low as 10% was also found to be associated with long-term transfusion therapy, and is now routine after stroke in children with SCD.[18,19] Despite the risks for a chronic transfusion program, including iron overload,[20] it became clear from a recent study that transfusions should be continued to prevent stroke in children with SCD. This clinical trial study has been highlighted in an online clinical alert issued by the National Heart, Lung, and Blood Institute of the USA (http://www.nhlbi.nih.gov/health/prof/blood/sickle/clinical-alert-scd.htm). Iron deficiency is another common pediatric problem, affecting 20-25% of the world's infants and is very prevalent among Saudi infants screened in a well-baby clinic.[21] There is a strong association between iron deficiency and cerebral ischemic events in children (8-18 months of age), but the mechanism remains to be defined.[22] Hemorrhagic stroke can complicate inherited or acquired hemorrhagic diatheses; these include deficiencies of factors VII, VIII, IX, X, XI, and XIII, as well as, hereditary platelet defects. Prothrombotic disorders[23-47] are important risk factors for the development of cerebrovascular ischemia/infarction during childhood.[20,24-26,48,49] They result from a shift of the normal hemostatic balance towards thrombosis, due to disturbances of the coagulation cascade, fibrinolytic system, the platelets or the vascular endothelium.[20] An overall incidence of prothrombotic states ranging between 10-50% was reported in children with ischemic strokes.[23,50,51] A hypercoagulable state, whether acquired or inherited, is also important in the pathogenesis of cerebral venous thrombosis (CVT) in children[52] and, in one study, inherited hypercoagulable disorders were present in 31%.[53]

The prothrombotic risk factors in childhood stroke include reduced levels of the natural coagulation inhibitors (antithrombin III, proteins C and S, and heparin cofactor-II),[23,25,26,31-33,37-44] plasminogen[23,31] and the presence of antiphospholipid antibodies (APAs), either circulating lupus anticoagulants (LA) or anticardiolipin antibodies (ACLA).[23,27,31,34,45,54,55] Recently, activated protein C (APC) resistance (with and without the genetic defect of factor V Leiden), prothrombin gene G20210A mutation[31,37,38,56] and homocysteinemia[31,56] (resulting from mutation of the gene encoding the enzyme 5, 10-methylenetetrahydrofolate reductase) have emerged as further pathological conditions associated with familial thrombophilia[28,29] and venous thrombosis,[30,31] and as causes of childhood stroke.[23,28-33,35,37-40,43,56] Other prothrombotic states associated with childhood stroke include elevated levels of markers of thrombin generation (thrombin - antithrombin complexes [TAT], prothrombin fraction 1+2, D-Dimer),[33] factor VIII and lipoprotein-a (Lp-a)[31,37,51,57] A recent literature survey uncovered some disagreements on the contribution of these prothrombotic states to the etiology of childhood stroke. Most studies found prothrombotic states are closely associated with the occurrence of childhood stroke and, therefore, recommended screening these patients for evidence of such heightened tendency to intravascular cerebral thrombus formation. The 3 discrepant studies[34,37,38] were not able to find abnormal plasma levels of natural anticoagulants or other markers of a hypercoagulable state in children with stroke, when compared to healthy controls, and therefore, they came to the conclusion that routine screening for prothrombotic markers is not justified. Nonetheless, most recent studies did implicate thrombophilia as causative of childhood ischemic stroke and CVT.[58,59] Deficiencies of the natural anticoagulants, protein C, protein S and antithrombin III, may be inherited or acquired. Infections, disseminated intravascular coagulation (DIC), hepatic

failure, renal disease and certain medications such as L-asparaginase are the most common causes of acquired deficiencies.[20] Cerebral venous thrombosis has also been reported in children with nephrotic syndrome[60] and is commonly attributed to renal loss of coagulation inhibitors.[61] Factor V Leiden gene mutation, which accounts for 90-95% of all activated protein C resistance,[62] has been observed in 5-12% of the general pediatric population.[63] The APAs are a heterogeneous group of antibodies which are directed against cell surface phospholipid moieties shared by platelets, coagulation factors and endothelial cells. They are either IgG or IgM antibodies and can be measured in the laboratory as LA and ACLA; both are recognized risk factors for transient ischemic attacks and stroke.[64] The ACLA IgG class, in particular, has a strong link to cerebrovascular disease.[64] Systemic lupus erythematosus (SLE) is the main disease known to be associated with APAs. Lupus anticoagulant was detected in 39% of SLE patients, and 43% of these were reported to have ACLA.[65,66] Lupus anticoagulant inhibits the prothrombin activator complex, prolongs partial thromboplastin time (PTT) and by name would be expected to promote hemorrhage. However, in the absence of an associated thrombocytopenia, patients with LA are more likely to develop either arterial or venous thrombosis rather than hemorrhage.[67,68] The presence of LA has also been found to be associated with collagen-vascular diseases, drugs, neoplasms and has been reported as an isolated finding.[68-70] An associated diminished protein C or S levels has also been reported in 2 children who had APAs.[25] In each of 2 other children with LA, there was also family members with APAs.[71] However, Mueh et al[69] described 3 children with transient LA following infection. Although McColl et al[72] did not find an increased prevalence of ACLA in children with stroke in a case control study, others[73] found that the presence of APAs conveys a stroke risk 10 times that seen in patients without APAs. The present study explores the hematologic risk factors for stroke in a cohort of 104 Saudi children, who were seen during a retrospective and prospective study on childhood stroke spanning 10 years and 7 months.[74]

Methods. This study is composed of 2 groups, the retrospective study group (RSG): including children with stroke (aged one month - 12 years) who were evaluated at the outpatient clinics, Division of Pediatric Neurology (DPN), or inpatients admitted to the Pediatric Wards at King Khalid University Hospital (KKUH), College of Medicine, King Saud University (KSU), Riyadh, during the period July 1992 and February 2001. The prospective study group (PSG) includes those patients who were seen between February 2001 and March 2003. Neuroimaging for suspected cases of stroke consisted of cranial CT, or MRI, or both, magnetic resonance angiography (MRA), cerebral and aortic digital subtraction angiography, as detailed elsewhere.[74] Screening children with SCD by TCD studies (using DWL, Multi Dop X4, Germany) and Duplex scan (HDI 5000, ATL, USA) became available during the last 4 months of the prospective study.[74]

Hemostatic assays. Most of the hemostatic assays were well established in the Coagulation Laboratory, College of Medicine, KSU, while others were started during the prospective study period. They included coagulation screening tests, tests of thrombin generation and fibrinolysis, coagulation inhibitors assay and other specialized tests. Coagulation screening tests consisted of prothrombin time (PT) and activated partial thromboplastin time (APTT) (Manchester Comparative Reagents, UK.); thrombin time (TT) (Park Davis Topical Thrombin, USA); reptilase time (RT) (Stago Diagnostics, France); and plasma fibrinogen, which was assayed by the turbidimetric method of Ellis and Stransky.[75] Thrombin-antithrombin complex (TAT) and fibrinopeptide A (FPA) and prothrombin fraction 1+2 (F1+2) were assayed by the enzyme-linked immunosorbent assay (ELISA) technique using kits supplied by Behring Mannheim, Germany. The plasminogen activator inhibitor (PAI) was assayed by ELISA technique using kits supplied by Stago Diagnostics, France. Protein C and protein S (total) were assayed by ELISA techniques and antithrombin III by a chromogenic assay (Stago Diagnostics, France). Activated protein C resistance was measured using the functional clotting assay [Stago Diagnostics, France].

Statistical analysis. The Stat Pac Gold Statistical Analysis Package was used for data management. Paired t-test (2-tailed) and Fisher's exact test were used for comparison of data among the different groups. A probability value of <0.05 was considered to be significant.

Results. During the study period, 104 Saudi children with stroke were seen. The mean age of the cohort was 27.1 months (SD = 39.3 months) and median was 6 months. Ischemic strokes accounted for the majority (76%) of cases. A major risk factor could be identified in 93 of cases (89.4%).[74] Hematologic disorders were the most commonly identified group of risk factors. Prothrombotic disorders took the highest share (33 of 104, 31.7%). Microcytic hypochromic anemia was detected in 27 patients

(26%), SCD in 12 (11.5%) and congenital deficiency of coagulation factors in 3 (2.9%). **Table 1** shows the results of the 33 patients with positive laboratory test results for a prothrombotic disorder. The presence of ACLA was the most frequent abnormality and was an isolated finding in 7 (14%) patients. The ACLA was associated with other prothrombic abnormalities in 6 children including protein C deficiency (n = 2), protein S deficiency (n = 2), and combined protein C and protein S deficiencies (n = 2). Of the natural anticoagulants, protein S deficiency (15/70, 21.4%) was more prevalent than protein C deficiency (11/70, 15.7%). Combined deficiency of 2 or more of the natural anticoagulants (protein C, protein S and antithrombin III) was detected in 6/70 (8.6%) patients. These included protein C and protein S (n = 5) and antithrombin III, protein C, and protein S (n = 1). Activated protein C resistance was not detected in any of the 18 patients in whom the assay was performed. No significant association was found between the presence of ACLA or a deficient natural anticoagulant (protein C, protein S or antithrombin III) and abnormalities in red blood indices, erythrocyte sedimentation rate (ESR), PT, fibrinogen, antinuclear antibodies (ANA), Mycoplasma pneumoniae IgM antibody and brucella antibodies. Of the 33 blood samples that revealed prothrombic abnormalities, 29 (87.9%) were taken 2 or more months after the event of stroke, one at 2 weeks and 3 within one week of the stroke. A positive family history of stroke was present in 2 of the 33 children with a prothrombic abnormality. One is a 10-year-old boy who had an arterial ischemic infarct, associated with both low protein C and protein S as well as ACLA (assayed within the first week of the ischemic event). His 25-year-old sister (who had been seen at another hospital) died shortly after a massive stroke (MCA territory infarct), following a respiratory tract infection. This patient was seen towards the end of the study period and was not available for follow-up to ascertain the presence of genetically inherited prothrombic disorders. The other patient was a 7-year-old girl who had recurrent strokes and MMS associated with protein S deficiency. At the time of writing this communication, we learned that one of her maternal cousins (who was born at another hospital) had a stroke shortly after birth.

Sickle cell disease. Sickle cell disease (SCD) constituted 11.5% of the identified risk factors in the 104 Saudi children. The ages of the 12 affected patients (**Table 2**) ranged between 3 years and 11 months and 12 years (mean = 97 months, median = 99.5 months), when they were first evaluated at the DPN. Of these 12 patients, 4 have been in the PSG of 23 Saudi children, whereas the others belonged to the 81, who constituted the RSG. No significant difference was found between the proportions of cases detected during the prospective or retrospective periods of study. The initial cerebral insult occurred, or was detected by MRI, at ages ranging between 3 and 12 years (mean = 88.5 months, median = 94.5 months). Three patients had history of recurrent strokes, whereas another 3 had no gross motor deficit and were first identified by TCD, followed by neuroimaging.

Other confounding hematologic and cardiac factors were detected in 3 patients. These included a 5-year-old boy (Patient 1, **Table 2**) who had multiple strokes and SCβ^0-thalassemia (SCβ^0-thal), associated with membranous ventricular septal defect. In this patient, MRA revealed occlusion of both ICAs, at the level of the suprasellar region with early moyamoya changes (**Figure 1**). The posterior circulation was spared. The second patient was a 12-year-old boy who had associated trivial pulmonary valve regurgitation, detected by echocardiography, but normal cardiac function. His ECG was also normal. The third child (the sibling of the second patient) was an 11-year-old boy who had SCD (diagnosed at 7 months of age) associated with Glanzmann thrombasthenia, which has been diagnosed when he was 3 months old.

Three of the 12 (25%) children with SCD belonged to one consanguineous family. These included the above-mentioned boy who had Glanzmann thrombasthenia, no discernible motor deficit, but recurrent headaches. Transcranial Doppler detected a velocity of 180 cm/sec in the left distal ICA. Cranial MRI showed multiple lacunar infarcts, whereas MRA of the brain and neck vessels revealed no abnormalities. His elder 12-year-old brother (Patient 2, **Table 2**) also had SCD, diagnosed at the age of 7 months, but no detectable motor deficits. However, screening with TCD revealed high flow velocities associated with moderate to severe stenosis of the anterior circulation vessels (at the internal carotid bifurcation, bilaterally). Following these findings, an MRI revealed an old infarct in the left cerebral hemisphere, whereas MRA showed marked narrowing of the left ICA associated with complete occlusion of the supraclinoid and intra-cavernous portion of the left ICA and left MCA. Their elder sister (Patient 4, **Table 2**) had multiple strokes since the age of 42 months. She was diagnosed to have SCD at 7 months of age, and following the first stroke, she was enrolled by the Division of Pediatric Hematology for a regular monthly blood transfusion, for 3 years. Cranial MRI (at the age of 7 years) showed an old infarct in the territory of the left MCA. Following another episode of stroke at the age of 10½ years, she had cerebral angiography, which revealed

Table 1 - Prothrombolic testing in Saudi children with stroke.

Prothrombolic test	No. of patients tested	Patients with abnormal results N (%)
Anticardiolipin antibodies	49	13 (26.5)
Protein S	70	15 (21.4)
Protein C	70	11 (15.7)
Antithrombin III	70	1 (1.4)
Activated protein C resistance	18	0 (0)

Table 2 - Clinical characteristics of patients with sickle cell disease.

Patient	Gender	Age at onset of initial stroke (years)	Age when evaluated at DPN (years)	Type of stroke	Other risk factors or associated findings	Recurrence of stroke	Duration of follow-up (years)	Outcome
1	M	3	5	Arterial ischemic: Bilateral ICA, MCA, ACA occlusions. Early moyamoya changes	SCβ^0 - thalassemia + membranous VSD	Yes (moyamoya syndrome)	7.5	Alive
2	M	12	12	Arterial ischemic: Left ICA and left MCA occlusions.	Trivial pulmonary regurgitation	No	0.3	Alive
3	M	11	11	Multiple lacunar infarcts	Glanzmann thrombasthenia	No	0.4	Alive
4	F	3.5	8.5	Arterial ischemic: Left cortical + moyamoya syndrome	No	Yes (moyamoya syndrome)	13.5	Alive
5	M	8	8	Lacunar infarcts: Bilateral frontal. Bilateral ICA stenosis	No	No	1.2	Alive
6	F	9.9	9.9	Arterial ischemic	No	No	2	Died of acute chest syndrome
7	M	5.8	5.8	Arterial ischemic: Right cortical infarct	No	No	2	Alive
8	F	8.6	8.6	Arterial ischemic: Left cortical infarct	No	No	Lost to follow-up after discharge from hospital	Alive on discharge from hospital
9	M	6.1	7.4	Arterial ischemic: Right cortical infarct	No	No	0.5	Alive
10	F	9	9.1	Arterial ischemic: Multiple infarcts affecting bilateral parietal lobe and left frontal lobe	No	No	1.3	Alive
11	M	7.8	8	Arterial ischemic: Left parietal infarct	No	No	Lost to follow-up after discharge from hospital	Alive on discharge from hospital
12	F	3.9	3.9	Hemorrhagic infarct of the right fronto-temporal lobe	No	No	10	Alive

DPN - Division of Pediatric Neurology, ICA - internal carotid artery, MCA - middle cerebral artery, ACA - anterior cerebral artery, VSD - ventricular septal defect

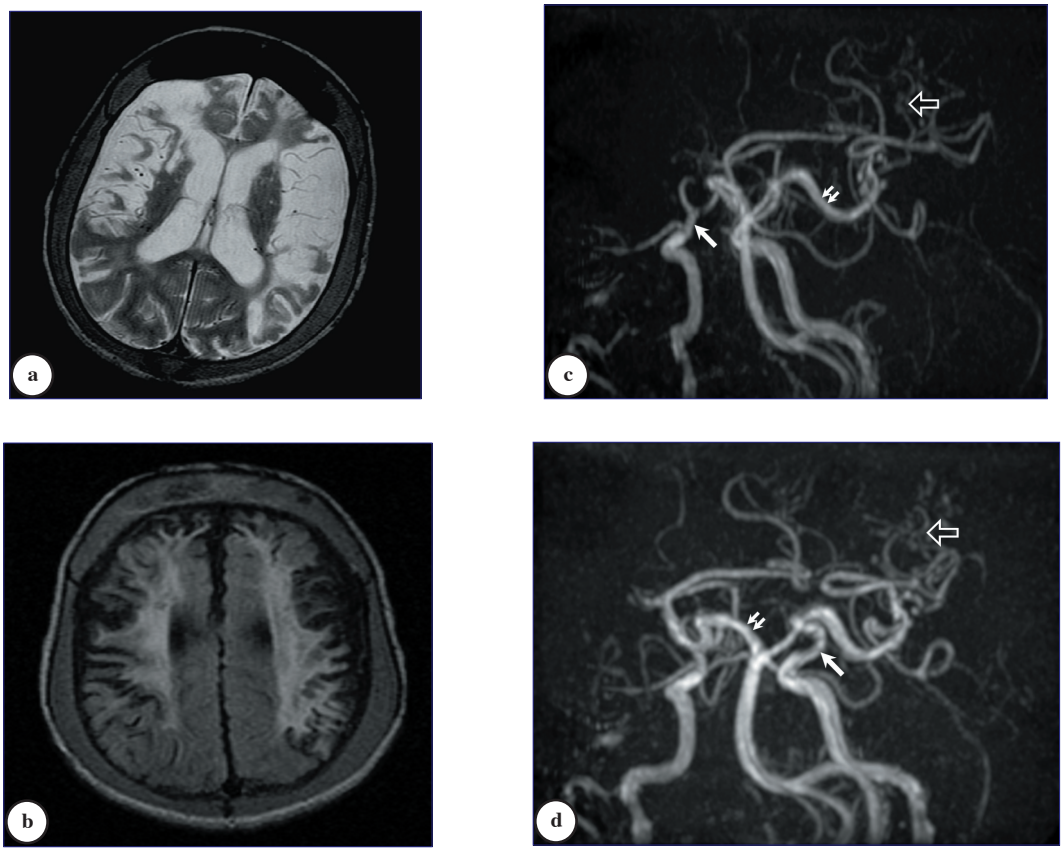

Figure 1 - a) Axial T2-weighted brain MR image and **b)** Axial fluid-attenuated inversion recovery (FLAIR) image showing right frontal and left frontoparietal cystic encephalomalacia and gliosis due to old infarction, as well as thick diploic space. **c & d)** MR angiography showing severely attenuated caliber and occlusion of the distal part of both internal carotid arteries (arrow) with normal caliber of both posterior cerebral arteries (double small arrows) and dilated collaterals (open arrow).

features of MMS (**Figure 2**). She became aphasic and had significant cognitive deficit. Her neurological condition improved following revascularization surgery (encephaloduroarteriosynangiosis).

The third child with SCD, whose vascular pathology was revealed after the application of TCD (during the last 4 months of the study), was an 8-year-old boy (Patient 5, **Table 2**). He presented with migrainous headaches since the age of 7 years but no motor deficits. Electroencephalography was normal during the awake and drowsy state. Transcranial Doppler screening revealed velocity of 180 cm/second in the right distal ICA, and 250 cm/second in the left ICA. There was evidence of moderate to severe stenosis of the left ICA (60%) and severe stenosis of the right ICA (70%). Duplex scan of ICA revealed severe bilateral tortuosity but no extracranial stenosis. Angiography showed tortuous cervical portions of both ICA and focal short narrowing (>50%) at C3 level, on both sides. Brain CT showed no evidence of an abnormal area of altered attenuation, whereas MRI revealed bilateral frontal lacunar infarcts.

Congenital deficiency of coagulation factors. Congenital deficiency of coagulation factors was identified as a risk factor in 3 children, all of whom had hemophilia B (factor IX deficiency). Two of these were siblings.

Patient One. This was the older of the 2 siblings and presented to KKUH in Riyadh at the age of 5 years. He was referred from a regional hospital in Buraidah 5 days after sustaining an intracranial bleed. He had been diagnosed at the age of 14 months to have hemophilia B (factor IX = 1.7%). There was a family history of a maternal uncle who died of the disease. He presented to the hospital in Buraidah 3½ hours after the onset of symptoms and received factor IX boluses. Two days later, he was transferred to KKUH for further management. Cranial CT scan showed massive right parieto-occipital intracerebral acute hematoma. He was declared brain dead after 3

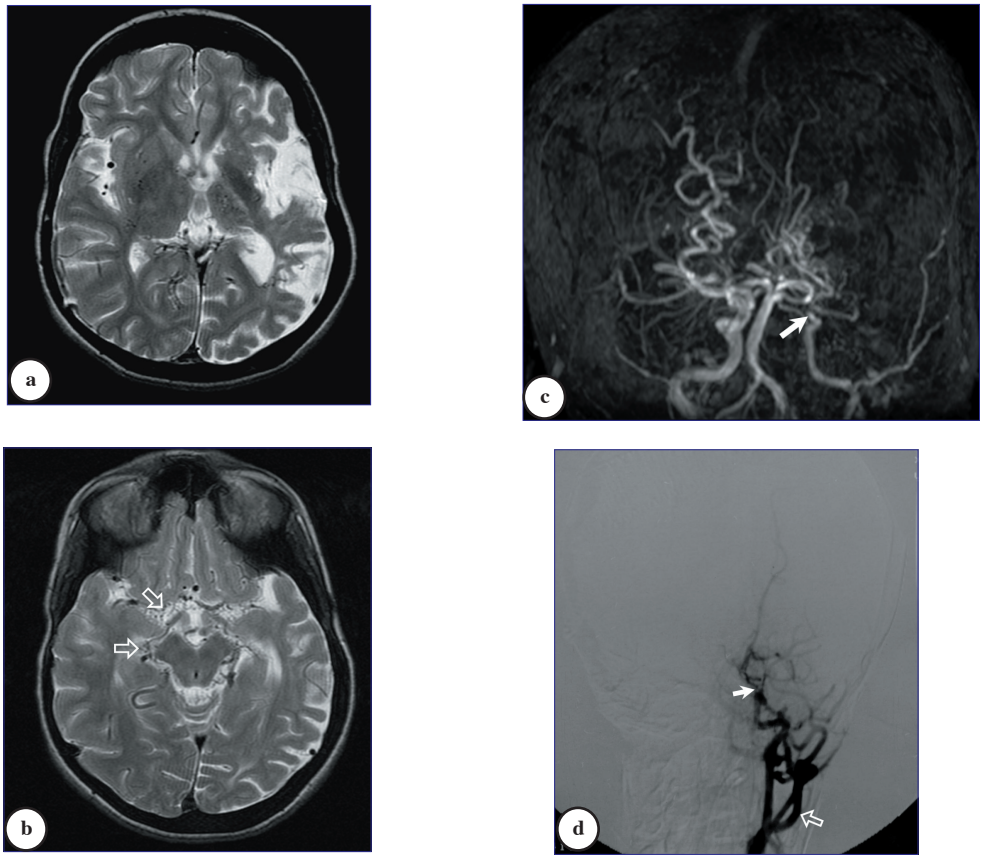

Figure 2 - **a)** Axial T2-weighted image (T2WI) of the brain showing left temporal and left parietal cortical high signal intensity due to infarction. **b)** Axial T2WI depicting multiple signal voids in the basal cisterns (open arrows) due to dilated collaterals. **c)** MR angiography showing attenuated caliber of the left internal carotid artery more distally (arrow) with marked narrowing of the origin of left anterior and middle cerebral arteries. Attenuated caliber of the left posterior cerebral artery with multiple dilated collaterals is also shown. **d)** Digital subtraction cerebral angiogram showing the markedly attenuated caliber of the left internal carotid artery more distally (arrow) with non-visualization of the anterior and middle cerebral arteries. Open arrow points to the external carotid artery.

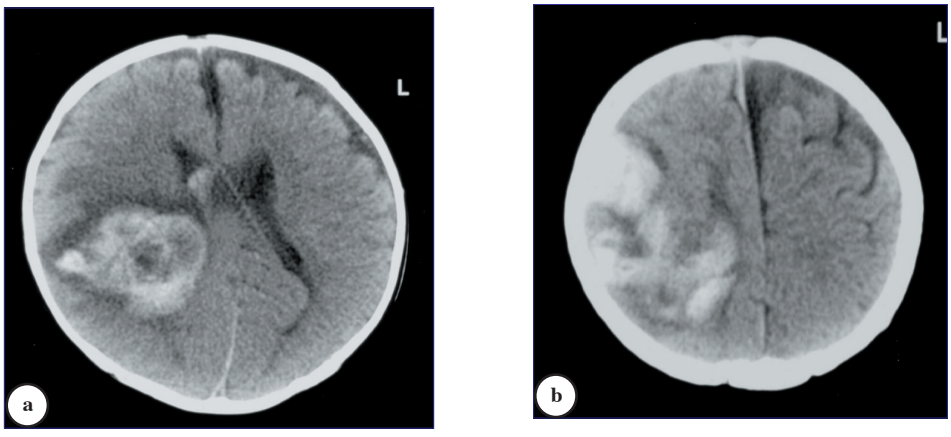

Figure 3 - **a)** Axial brain CT showing large right parietal high attenuation lesion due to acute intracerebral hematoma with associated mass effect on the right lateral ventricle and mild midline shift towards the left side. Note the intraventricular bleeding in the right frontal horn. **b)** Axial brain CT showing extension of the acute intracerebral hematoma to the right frontal lobe.

days of management at the Pediatric Intensive Care Unit (PICU). Both electroencephalography (EEG) and brain auditory evoked potentials (BAEP) were flat, whereas single photon emission tomography (SPECT) showed empty skull (the sign of brain death).

Patient 2. After 6 years and 5 months from the death of his sibling, the younger brother of Patient 1 presented (when aged 5 months) to KKUH 5 days after the onset of a febrile illness associated with recurrent seizures, which were initially generalized and then evolved into recurrent left focal seizures. This was followed 3 days later by left hemiparesis. He also had vomiting and became irritable. Family history was positive for recurrent febrile convulsions. Apart from pyrexia, initial clinical examination documented an altered level of consciousness (drowsiness), macrocephaly (skull circumference = 46 cm >95th centile), right occulomotor nerve palsy, and left hemiparesis. Cranial CT scan (**Figure 3**) showed a huge right parietal and parieto-occipital hematoma with fluid level and midline shift. There was also mass effect on the midline structures. Brain SPECT showed high attenuation nodule in the right parietal region. Hematologic investigations showed raised WBC of 15.4 x 10^9/L, normochromic normocytic anemia (Hb = 70g/L), thrombocytosis (platelet count = 505 x 10^9/L), raised ESR (27 mm/hr), normal PT, prolonged APTT (86.8 sec, control = 26-38), and elevated fibrinogen level (5.35g /L, N=2-4). After giving the patient fresh frozen plasma (FFP), factor assays showed normal factor VIII of 109% (N=50-200%) and low factor IX of 26% (N=50-150%). The child received blood transfusion and underwent urgent craniotomy and evacuation of the intracranial hematoma. He also received FFP and repeated factor IX infusions, as indicated. He made an excellent recovery with no residual motor deficits detected after 2 years but only myoclonic seizures, which have been well controlled on sodium valproate. Brain MRI (8 months after the intracranial bleed) showed moderate-sized right parietal parenchymal loss.

Patient 3. This 11-month-old boy was evaluated at the DPN because of right-sided hemiplegia and epilepsy. Reviewing his medical history, he was found to have been admitted to one of the pediatric hospitals in Riyadh at the age of 6 months with irritability, seizures, right-sided hemiplegia and decreased level of consciousness. Cranial CT showed left subdural hematoma. Investigations revealed factor IX deficiency, and family history was positive for hemophilia B in 3 of his maternal uncles.

Discussion. Prothrombotic disorders, whether inherited or acquired, are becoming increasingly recognized as an important risk factor for childhood stroke.[20,48,59] In children with ischemic stroke, an overall incidence of prothrombotic states ranging between 10-50% has been reported in several studies.[23,50,51,76] These prothrombotic disorders have also been identified as important underlying factors in the pathogenesis of cerebral venous thrombosis.[52,53,58] In the present study, approximately one third of children (31.7%) had one or more abnormal test results for a prothrombic condition. This is similar to the figure of 38% which has been found by de Veber et al[23] in a prospective study of 92 patients (newborns to 18 years) with arterial ischemic stroke or sinovenous thrombosis. In our patients, the presence of ACLA was the most prevalent associated risk factor (26.5%). Anticardiolipin antibodies were found in up to one third of children with stroke, but their presence does not predict recurrence of stroke.[23,77] Regarding natural anticoagulants, protein S deficiency (21.4%) was more prevalent than protein C deficiency (15.7%). Antithrombin III was deficient in only one patient and activated protein C resistance was not detected in the 18 children in whom the test was carried out. These findings are generally similar to those reported in 40 Saudi adults who had cerebral venous thrombosis.[78] In this study, none of the patients had protein C deficiency, whereas deficiencies of protein S was detected in 3 patients and antithrombin III in 2 patients. Activated protein C resistance was not explored. In another study,[79] on primary thrombophilia in adult patients with extracranial thromboembolism, protein S deficiency was also the most common identified abnormality (14.5%), followed by protein C (8.4%), while antithrombin III was not deficient in any of the 179 tested subjects. Activated protein C resistance was present in only 4 patients (2.2%). We are not aware of any previous study on the role of these natural anticoagulants in the pathogenesis of stroke in Saudi children. However, there is a case report[80] on 2 full-term newborn infants who had cerebral infarction associated with combined deficiencies of protein C, protein S and antithrombin III. In both cases, maternal and neonatal serum anticardiolipin, antinuclear, and anti-DNA antibodies were not detected. In the present study, 6 children (8.6%) had combined deficiencies of antithrombin III, or protein C, or both, and protein S and this is similar to the observations in other large series.[23] It is known that most coagulation disorders underlying arterial ischemic strokes are acquired,[81] and usually compound other risk factors.[31] However, abnormalities in Lp-a and protein C were reported to predict recurrent stroke.[82] Repeated testing after 6-8 weeks helps to exclude secondary as opposed to primary deficiencies of protein C, protein S and

antithrombin III, transient elevations of APAs and acute phase elevations of Lp-a.[49] The majority of patients in the present study (87.9%) had their blood tested for hypercoagulability 2 or more months after the event of stroke. In the present study, 2 of the children who showed deficiencies of one or more of the natural anticoagulants had a family history suggestive of an inherited primary thrombophilia. Congenital deficiency of protein C, protein S and antithrombin III are inherited as autosomal dominant and heterozygous individuals are at risk of thrombosis and thromboembolism.[83] In such cases, family studies are invaluable in assessing the chance of other children within a given family of having an inherited plasma-phase risk factor. In the present cohort, the family of the first child was counseled on the importance of this screening but the parents declined the investigations. In the second child, the family history was revealed following the birth of an affected baby after the end of the study. The exact frequency of congenital prothrombic conditions in Saudi children is difficult to determine from our study because not all patients were investigated simultaneously for all abnormalities. Moreover, family studies were not performed previously. A number of plasma-phase risk factors were not explored, including the prothrombotic genetic defects such as factor V Leiden, prothrombin gene G20210A mutation, the enzyme 5, 10-methylenetetrahydrofolate reductase gene mutation, Lp-a levels and high factor VIII.[49,59] Nonetheless, the results of the present study highlighted strongly the importance of prothrombotic disorders as a risk factor for stroke in Saudi children. Large prospective follow-up studies will be needed to evaluate all children with stroke for prothrombotic conditions and investigate their families if persistent abnormalities were identified. Such an approach will ensure that more children will benefit from the specific, appropriate treatments designed to prevent stroke and its recurrence.[49]

A strong association between iron deficiency and cerebral ischemic events in children has been reported, but the mechanism remains to be defined.[22] In the present study, hypochromic microcytic anemia was found in 27 patients (26%). The overall prevalence of anemia in Saudi children was reported to be 24.8%.[84] The major type of anemia in the eastern and south-western provinces is hypochromic microcytic and is thought to reflect the high prevalence of both thalassemias and iron deficiency in these regions.[84] In a recent study,[58] on 42 children with cerebral venous sinus thrombosis from 5 European pediatric neurology stroke registries, anemia, or microcytosis (21 probable iron deficiency, 5 hemolytic, including 2 with SCD and one with β-thalassemia), was as common as prothrombotic disorders. Whether iron deficiency is a significant confounding variable in the development of stroke in Saudi children, awaits to be clarified in future studies.

Cerebrovascular disease is a major cause of morbidity and mortality in SCD. Approximately 10% of patients will manifest a clinical stroke by the age of 20 years, and another 22% develop silent infarct on MRI.[85,86] The pathophysiology of cerebrovascular disease may involve stenosis of large arteries of circle of Willis associated with progressive development of lenticulostriate collateral vessels manifesting as moyamoya pattern on neuroimaging and watershed ischemia.[81] In the present study, SCD was the fifth ascertained risk factor and was identified in 11.5% of the 104 Saudi children with stroke. Previous smaller studies in Saudi Arabia revealed a low frequency of SCD in stroke patients from the Eastern Province. In one study,[87] it accounted for one of 21 (4.8%) children and one of 31 (3.2%) in another.[88] Sickle cell disease, like many other single gene disorders, has significant phenotypic heterogeneity. These are thought to be due to the effects of modifier genes, as well as environmental factors.[1,89] Two different phenotypes of SCD can be identified in Saudis. In the Eastern Province, the disease is mild, whereas in the Western Provinces it runs a severe course.[90] Molecular studies[91] uncovered 2 major haplotypes of the ß-globin chain. One in the Eastern Province of Saudi Arabia (Arab-Indian haplotype), which manifests with mild clinical presentation, and another one in the populations of north-western and south-western parts of the Arabian Peninsula, and in Arab populations in North Africa (Benin haplotype). The latter haplotype presents with severe manifestations of SCD. In a study on SCD patients from Kuwait,[92] the Arab-Indian haplotype was the most common (80.4%), while the Benin haplotype constituted only 12%; patients with Arab-Indian haplotype had HbF ranging between 11.4-35.1% (mean ± SD: 22.5 ± 5.2%). The frequency of alpha-thal determinants in this study was 40%. The authors concluded that both the high frequencies of the Arab/Indian haplotype and alpha-thalassemia trait contribute to the mild nature of SCD among Kuwaiti Arabs, comparable to that in eastern Saudi Arabia. Coinherited α-thalassemia seems to confer protection from stroke possibly by improving RBC deformability and decreasing hemolysis.[93] Another important genetic modifier for SCD severity is the presence of *Xmn*1 5' to Gg polymorphic site, which is associated with mild clinical presentation. This polymorphic site was present in 90% of the chromosomes investigated in SCD patients in Eastern Saudi Arabia, whereas it

was absent in 96.6% of patients from the southwest region.[94,95] The Cooperative Study of Sickle Cell disease (CSSCD), a national, multicenter study designed to define the natural history of SCD in the USA, reported a higher prevalence of SENβ^s globin gene in SCD children with silent infarcts.[96] However, positive association with specific β^s globin haplotypes was not found in other studies.[3,97] Moreover, although the overall clinical course of SCD has been shown to improve with increased HbF, an association between low HbF levels and stroke or silent infarction has not been shown in several studies.[3,98] Other genetic risk factors leading to vasculopathy in SCD seem to have a significant role.[99] In the present study, 2 of the 12 patients with SCD had radiological evidence of MMS which was first diagnosed in children with SCD in 1972.[5] Its prevalence in SCD is as high as 43% in patients who had suffered strokes, while under the age of 18 years, despite their placement on chronic transfusions after stroke.[8] This correlated with the recent advent of MRA, which defines the pattern of vascular abnormality in a comparable way with conventional angiography. In the study of Dobson et al,[8] moyamoya patients were also more likely to have 2 or more recurrent cerebrovascular events (stroke or transient ischemic attack), as well as poor results of neuropsychological testing. It is noteworthy that one of the patients in this study (**Table 1**, Patient 4) developed her first stroke at the age of 3½ years, and was subsequently enrolled in chronic monthly blood transfusion for 3 years. At the age of 13 years, she developed a second stroke. Cerebral angiography revealed features of MMS. She had aphasia, dysphagia, and significant cognitive deficit. Her neurological condition improved following revascularization surgery (encephaloduro-arteriosynangiosis), which has recently been shown to be a safe and effective treatment option in patients with SCD who develop MMS.[100] The frequency of a first stroke in SCD is higher in early childhood; it was estimated to be 1.02 per patient – year from 2-5 years, 0.79 from 6-9 years, and 0.41 from 10-19 years.[3] Chronic transfusion therapy, aiming at maintaining sickle hemoglobin (Hb S) levels below 30%, can reduce the risk of recurrent stroke from 40-90% to approximately 10%.[85] A stroke recurrence rate of 70% was observed after the prospective discontinuation of a short-term (1-2 year) transfusion regimen,[101] while a recurrence rate of 50% was observed after prospective discontinuation of a long-term (5-12 year) transfusion regimen.[102] However, up to 41% of patients with SCD experience recurrent stroke or transient ischemic attacks after an initial stroke despite chronic transfusions and the risk is significantly higher for those who have moyamoya collaterals.[8] The hazards and limitations of long-term transfusion therapy should also be born in mind and these include the transmission of infectious agents, erythrocyte alloimmunization, iron over-load, difficulties with venous access, compliance and cost.[103-105] Recently, hydroxyurea, with or without phlebotomy, was used for prevention of stroke and the sequelae of iron overload.[103,105]However, and as mentioned earlier, it became evident that it is not safe to stop transfusions even if TCD has returned to the normal range. Although TCD screening for patients with SCD has only been introduced during the last 4 months of the study, it proved to be of great value in identifying cerebrovascular disease in 3 patients with SCD, who later proved to have associated MRI/MRA abnormalities. The risk of stroke in children who have abnormalities in TCD ultrasonography and MRI is higher than those with TCD ultrasonographic abnormality alone.[106,107] Children with both abnormalities should strongly be considered for prophylactic transfusion therapy. Another interesting observation in the present study was the finding of 3 siblings with cerebrovascular disease in association with SCD. Familial predisposition to stroke in HbSS has been documented.[108,109] In a study which included 42 siblings in which at least one sibling had a stroke, a pre-mutation test showed that the number of families in which 2 children had stroke was significantly larger than the number expected if strokes were randomly distributed among children in siblings.[108] In another study,[109] the presence of a sibling with an elevated blood flow velocity in the large cerebral arteries, detected by TCD, raised 50 times the likelihood of detecting an elevated cerebral blood flow velocity in other siblings with SCD. These findings were consistent with a familial predisposition to cerebral vasculopathy in SCD. Family size and the high degree of consanguinity in Saudi Arabia[110-112] are well-suited for family based association and linkage studies for identifying the genetic risk factors for stroke in SCD.[99] Such identification will allow for the early intervention with therapies, such as regular blood transfusions, hydroxyurea or bone marrow transplantation before the development of adverse neurologic or cognitive sequelae.[113,114] It is noteworthy that in a seminal recent study on genetic dissection and prognostic modeling of overt stroke in SCD, Sebastiani et al[115] found that 31 single nucleotide polymorphisms (SNPs) in 12 genes interact with fetal hemoglobin to modulate the risk of stroke. They validated their model in a different population and could predict the occurrence of stroke in 114 individuals with 98.2% accuracy.

Three children in the current study had hemorrhagic stroke due to hemophilia B (factor IX deficiency). Two of these were siblings, one of whom died following an intracranial bleed and the other was saved following surgical evacuation of an intracranial hematoma. There was a strong family history of a similar bleeding disorder in all 3 patients. The absence of hemophilia A (factor VIII deficiency) in this cohort reflects the epidemiological limitations of a hospital-based study. In the largest published series on hereditary bleeding disorders (HBD) from Saudi Arabia,[116] patients with hemophilia were the majority among all bleeding disorders. Forty-one patients had hemophilia A, and 16 had hemophilia B. The same study,[116] also highlighted the local difficulties faced in the diagnosis and management of patients with HBD since most of them came from rural areas and often made long journeys to come to Riyadh for treatment. Another recent study from the Eastern Province[117] on 54 patients with HBD, observed that hemophilia B cases (n = 2) were fewer than expected compared with hemophilia A (n = 39).

In conclusion, the present communication strongly highlights the importance of prothrombotic disorders as a risk factor for stroke in Saudi children. Contrary to previous similar studies from Saudi Arabia, SCD accounted for >10% of the ascertained risk factors and those patients also had severe manifestations, highlighting the severe phenotype of SCD which, in addition to the mild type, is also prevalent in Saudi Arabia.

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