Moyamoya syndrome as a risk factor for stroke in Saudi children

Novel and usual associations

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ABSTRACT

Objective: To report on moyamoya syndrome (MMS) as a risk factor for stroke in a prospective and retrospective cohort of Saudi children. The usual and novel associations of MMS in this cohort will also be described.

Methods: Children with stroke were evaluated at the Division of Pediatric Neurology at King Khalid University Hospital, College of Medicine, King Saud University, Riyadh, Kingdom of Saudi Arabia during the periods July 1992 to February 2001 (retrospective study) and February 2001 to March 2003 (prospective study). Investigations for suspected cases included hemostatic assays, biochemical, and serological tests. Neuroimaging included CT, MRI, magnetic resonance angiography (MRA), single photon computerized tomography (SPECT) brain scan and conventional cerebral angiography.

Results: Moyamoya syndrome was the underlying risk factor for stroke in 6 (5.8%) of the 104 children (aged one month to 12 years). They were 4 females and 2 males. Their first cerebral ischemic event occurred at a mean age of 45 months (median = 44 months, range 17-66 months). In all 6 cases, MMS was associated with an underlying hematologic abnormality or other diseases. Protein C deficiency was identified in one girl and protein S deficiency in another. Two patients had respectively, sickle cell disease (SCD) and sickle cell-ß-thalassemia (Sß^{O}-thalassemia), which had been associated in the latter with membranous ventricular septal defect. Adams-Oliver syndrome (AOS, OMIM 100300) was associated with MMS in an 18-month-old girl. A 4-year-old boy had wrinkly skin syndrome (WSS, OMIM 278250) phenotype. The association of MMS and protein C deficiency was first reported in this cohort of patients, whereas the association of the syndrome with WWS and AOS has not, hitherto, been described. The 3 patients who had MMS associated with protein C deficiency, SCD, and AOS underwent successful revascularization surgery in the form of encephaloduroarteriosynangiosis.

Conclusions: Moyamoya syndrome constitutes an important risk factor of stroke in Saudi children. Comprehensive clinical evaluation and investigations, including screening for thrombophilia and neuroimaging studies, are required for the primary diagnosis of the disease and for unraveling other diseases associated with MMS. This will help in managing these patients and in guiding genetic counseling for their families.

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Moyamoya syndrome (MMS) is an unusual form of progressive cerebrovascular occlusive disorder, characterized by the development of an abnormal vascular network at the base of the brain.[1]

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First reported in 1957 by Takeuchi and Shimizu, the syndrome was named as "moyamoya" by Suzuki in 1969.[2] Moyamoya, a Japanese word meaning "a puff smoke," is a descriptive term indicating the typical abnormal angiographic picture, consisting of abnormal net-like collateral vessels at the base of the brain seen in this disease.[1,3] The syndrome has been described in patients of all ethnic groups but remains rare outside Japan where it constitutes the most common pediatric cerebrovascular disease with a high rate (>7%) of familial cases.[1,4] It can be idiopathic or associated with several other acquired vasculopathies and genetic syndromes.[5-7] Reported associations with MMS include central nervous system infections (basilar meningitis, tuberculous meningitis, leptospirosis), neonatal anoxia, trauma, several hematologic disorders (sickle cell disease [SCD], ß-thalassemia, Fanconi anemia, factor XII deficiency), and miscellaneous other syndromes such as Down syndrome, Turner syndrome, Apert syndrome, Marfan syndrome and William syndrome.[5,8] Neurocutaneous syndromes known to be associated with MMS include tuberous sclerosis, neurofibromatosis, Ehlers-Danlos, hypomelanosis of Ito, and pseudoxanthoma elasticum. Recognized vascular associations include renal artery stenosis, coarctation of the aorta, cerebral dissecting and saccular aneurysms, fibromuscular dysplasia and inflammatory disorders of the circulatory system (polyarteritis nodosa). Other diseases that were reported to be associated with MMS include metabolic disorders (type 1 glycogenosis), NADH-coenzyme Q reductase deficiency, pyruvate kinase deficiency, brain tumors, and cranial irradiation therapy for optic pathway gliomas.[5,6] Increasing awareness of MMS and early diagnosis is important as surgical intervention, using a variety of revascularization techniques, was reported to halt progression of the disease and to reverse deficits in some patients.[9-12] In the present communication we explore the role of MMS as a risk factor for stroke in a cohort of 104 Saudi children, who were seen during a prospective and retrospective study on childhood stroke. Syndromes and diseases, which were found to be associated, in this cohort, with MMS will also be described.

Methods. Patients with MMS were identified from within a cohort of 104 Saudi children (aged one month to 12 years), who presented with stroke and were evaluated at the Division of Pediatric Neurology (DPN), or were inpatients in the Pediatric Wards at King Khalid University Hospital (KKUH), Riyadh, Kingdom of Saudi Arabia. The duration of the prospective study was 2 years (February 2001 to March 2003), whereas the retrospective study extended for 8 years and 7 months (July 1992 to February 2001). For each child with stroke, the salient clinical, neuroimaging, neurophysiological and laboratory data were retrieved in a specially designed comprehensive protocol. Details of these, as well as the laboratory methods are depicted elsewhere.[13,14]

Results. Of the 104 Saudi children (aged one month -12 years) with stroke who were seen during the study period, MMS was an identified risk factor in 6 (5.8%) patients (4 females and 2 males). Their ages, when first seen at the DPN, ranged between 18 months and 8.5 years (mean = 64 months, median = 66 months). Their first cerebral ischemic event occurred at a mean age of 45 months (median = 44 months, range 17-66 months). In all of these cases, MMS was associated with another disease or hematologic abnormality. A girl had protein C deficiency and another had protein S deficiency. Two patients had, respectively, SCD and sickle cell-ß-thalassemia (Sß^{O}-thalassemia), which had been associated in the latter with membranous ventricular septal defect (VSD). An 18-month-old girl had associated Adams-Oliver syndrome (AOS, OMIM 100300), whereas a 4-year-old boy had wrinkly skin syndrome (WSS, OMIM 278250) phenotype. A summary of their clinical characteristics is shown in **Table 1**.

Patient one (**Table 1**) was a 6-year-old girl who has been referred to the DPN due to recurrent episodes of left-sided hemiparesis for one year and hemiconvulsions for 5 months. These had been preceded by headaches, which were relieved by paracetamol and were not associated with vomiting or visual disturbance. Laboratory and radiological investigations (including conventional cerebral angiography) showed features of MMS associated with low protein C of 50% (N = 70-100%). Details of the clinical and radiological findings of this patient have been reported.[15,16] She was maintained on carbamazepine and aspirin and underwent surgical revascularization in the form of encephaloduro-arteriosynangiosis (EDAS) at the age of 13 years. The procedure and anesthetic considerations have also been described.[17] She remained well thereafter.

Patient 2 (**Table 1**) was a 7-year-old girl who was admitted to the pediatric wards of KKUH with history of headache and right arm weakness for 3 days. The headache was mainly in the occipital and temporal areas and was associated once with non-projectile vomiting. Her family became worried as she could no longer hold things with her right hand. On enquiry, she was found to have had recurrent episodes of similar headaches involving the temporal and occipital regions for the

Table 1 - Clinical characteristics of patients with moyamoya syndrome.

Patient	Gender	Age at onset of initial stroke (years)	Age when evaluated at DPN (years)	Types of strokes (s)	Underlying / associated conditions	Stenotic and occlusive changes on MRA / angiography	Surgical management	Outcome
1	F	5	6	Arterial ischemic: right parietal, right frontoparietal and right putamen. Bilateral parieto-occipital old infarcts	Protein C deficiency	Both ICAs and right ECA branches	EDAS	Alive
2	F	5.5	7	Arterial ischemic: left parieto-occipital and right parieto–occipital cortical infarcts	Proteins S deficiency	Both ACAs and MCAs. Right ECA, right superficial temporal branch	None	Alive
3	F	3.5	8.5	Arterial ischemic: left temporal and left parietal cortical infarcts	SCD	Left ICA, MCA, ACA and PCA	EDAS	Alive
4	M	3	5	Arterial ischemic: right frontal and left frontoparietal cystic encephalomalacia	Sickle cell – ß – thalassemia (Sß^0 – thalassemia) and membranous VSD	Both ICAs, MCAs and ACAs	None	Alive
5	F	1.4	1.5	Arterial ischemic: generalized brain atrophy. Cortical and subcortical encephalomalacia at temporal and occipital lobes. Left frontal and left parietal cortical infarcts	Adams – Oliver syndrome, iron deficiency anemia	Both ICAs, MCAs, ACAs, and PCAs. Both superficial temporal arteries	EDAS	Alive
6	M	3.8	4	Arterial ischemic: left frontal, left parietal and left temporo-occipital lobes, peritrigonal area bilaterally, periventricular and subcortical white matter	Wrinkly skin syndrome	Both ICAs, proximal MCAs and ACAs	None	Alive

DPN - Division of Pediatric Neurology, SCD - sickle cell disease, VSD - ventricular septal defect, MRA - magnetic resonance angiography, ICA - internal carotid artery, ECA - external carotid artery, ACA - anterior cerebral artery, MCA - middle cerebral artery, PCA - posterior cerebral artery, EDAS - encephaloduroarteriosynangiosis

last 18 months. These used to occur approximately 2-3 times/week with no aggravating factors and subsided after taking paracetamol. Eight months earlier, she had been evaluated at the ENT department as part of the work-up for recurrent headaches. She underwent tonsillectomy and adenoidectomy with little improvement. Developmental history was normal. However, her mother noticed deterioration in school performance during her last semester. On examination, she was conscious and alert. Abdomen, cardiovascular and respiratory systems were normal. Also, no abnormalities were found in the cranial nerves or on fundal examination. There was mild weakness (Grade 4 Medical Research Council) in the right upper and lower limbs associated with exaggerated deep tendon jerks and up-going right plantar reflex. Routine EEG showed relative left hemispheric slowing suggestive of left structural lesion. Visual evoked potentials (VEP) revealed normal results. Cranial CT scan showed 2 low attenuation areas seen on both cerebral hemispheres, the left one being larger than the right. There was no evidence of hemorrhage or calcification. Brain MRI showed apparently recent large cortical infarct in the left parieto-occipital region and a small cortical infarct in the right parieto-occipital region (**Figure 1**). Cerebral magnetic resonance angiography (MRA) showed narrowing of the terminal part of both internal carotid arteries in the region of the circle of Willis, as well as narrowing of the origin of both middle cerebral arteries. There were tortuous collateral vessels seen around the circle of Willis, both anteriorly and along the posterior cerebral vessels. The caliber of the basilar artery was normal. Eleven weeks later, a repeat MRI (**Figure 1**) showed the previously described cortical infarctions, along the parieto-occipital region to be significantly reduced in size and replaced by areas of gliosis. There were no appreciable changes demonstrated in the MRA findings. Five days later, bilateral internal and external carotid and right vertebral angiography was

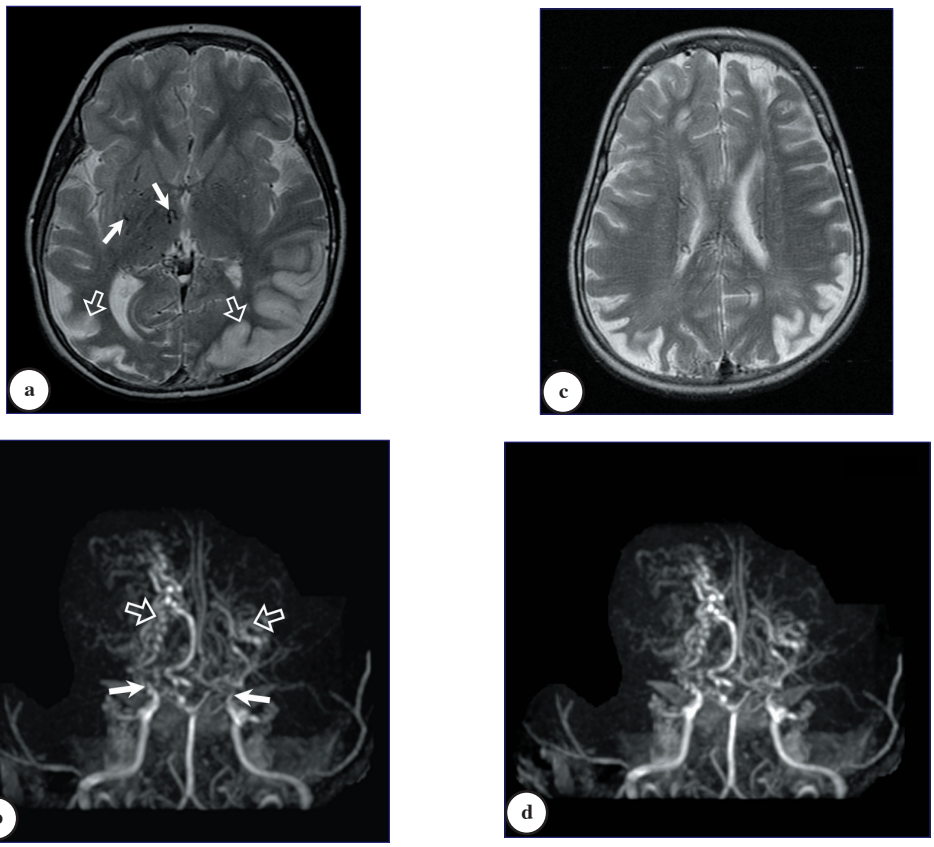

Figure 1 - a) Axial T2-weighted (T2W) MR image of the brain showing swelling of the left and right parieto-occipital gyri with increased signal intensity (open arrows) due to recent infarction. Multiple areas of signal voids (arrows) are seen in the region of the basal ganglia representing moyamoya vessels. **b)** MR angiography showing markedly attenuated caliber of the terminal part of both internal carotid arteries (arrows) in addition to the origin of both middle, both anterior cerebral, and posterior cerebral arteries. There is dilatation of the thalamoperforators and collateral formation (open arrows). **c)** Eleven week follow-up axial T2W MRI showing significant reduction in the size of the parieto-occipital infarction. **d)** The follow-up MR angiography shows no interval changes.

carried out for the patient. It confirmed the appearance of moyamoya disease, being more severe on the right side. There was stenosis of the left anterior and middle cerebral arteries, which were partially filled retrogradely through collaterals. The right anterior and middle cerebral arteries were occluded without any retrograde filling. The posterior cerebral arteries were dilated and ended in a meshwork of multiple collaterals around the ambient cisterns. There was poor opacification of the right external carotid artery (ECA) with severe attenuation of the right superficial temporal branch. The left ECA and branches were normally opacified. Hematologic investigations included complete blood count which showed normal hemoglobin (Hb) of 121g/L but low mean corpuscular volume (MCV) of 68 ft (N = 80-91) and mean corpuscular hemoglobin (MCH) of 21.3 pg (N = 23-31). Platelets were normal (384 x 10^9/L) and red cell distribution width (RDW) was raised at 15.1% (N = 11.5–14.5%). Protein S was significantly reduced at 17% (N = 65-140%) whereas both protein C (96%) and antithrombin III (105%) were normal. Several other hematologic, serologic and biochemical investigations either revealed normal results or were reported to be negative. These included erythrocyte sedimentation rate (ESR), prothrombin time (PT), activated partial thromboplastin time (APTT), Hb electrophoresis, antinuclear antibodies, double stranded DNA antibody, brucella antibody titers, antistreptolysin O titre, lipid profile (triglycerides and cholesterol), random blood glucose, serum lactate, and serum amino acid profile. She was maintained on a low dose of aspirin and over 46 months she remained to have right-sided hemiparesis, recurrent headaches, poor speech and progressive difficulty at school. The possibility of surgical intervention was discussed thoroughly, and on several occasions with the family, but they decided against surgery.

Patient 3 (**Table 1**) was referred to the DPN at the age of 8½ years. She was diagnosed to have SCD at 7 months of age and sustained a stroke at 3½ years, which presented as headache, right-sided weakness (including the face) and was followed by impairment of speech. Following this stroke, she was enrolled by the Division of Pediatric Hematology for monthly regular blood transfusion for 3 years. During the first assessment, her right-sided hemiplegia was ascertained and she had a brain MRI. This showed features of an old infarct in the territory of the left middle cerebral artery (MCA) with corresponding shift of the midline to the left, associated with left-sided encephalomalacia and ventricular dilatation. She was enrolled in a rehabilitation program, but she could not adhere to it regularly. After 4 years, she sustained another stroke resulting in aphasia, dysphagia that required nasogastric tube feeding, and atypical absence seizures. However, following physiotherapy, she could walk with right-sided hemiplegic gait. She continued to have recurrent headaches, and psychometry revealed mild mental retardation (IQ = 66-70%). Conventional cerebral angiography, following repeated blood transfusions, showed classical features of MMS. Several routine and special investigations were either negative or revealed normal results. These included PT, APTT, protein C, protein S, antithrombin III, blood culture, CSF examination, ECG, echocardiography, VEP, electroretinogram and brain auditory evoked potentials. Routine EEG showed generalized 2.5 Hz spike-wave activity with slowing mainly in the left hemisphere. Repeated EEG also revealed features consistent with Lennox-Gastaut syndrome. She underwent surgical revascularization (EDAS) at the age of 11 years and 2 months with good recovery. Of the residual sequelae resulting from the repeated strokes, recovery from dysphagia after surgery was the most remarkable, since she could maintain her nutrition without nasogastric tube feeding. An MRA, repeated 2½ years later, showed the moyamoya vessels and no definite signs of improvement or deterioration compared with the cerebral angiogram that had been carried out at the time of operation.

Patient 4 (**Table 1**) was seen at the DPN (when aged 5 years) due to right-sided weakness and epilepsy. He was known to have sickle cell-ß-thalassemia (Sß^{O}-thalassemia) and membranous VSD. Neurological history revealed that he had a febrile convulsion at 2 years and a stroke at 3 years of age. The latter one presented with generalized seizures, right hemiparesis and was followed by aphasia. Cranial CT showed prominent cerebral sulci and cortical atrophy especially at the parieto-frontal regions (more prominent in the left than the right side). On clinical assessment, he was found to have residual right-sided hemiplegia associated with bilateral pyramidal tract signs (pseudobulbar syndrome). He was also aphasic, had remarkable cognitive deficits and complex partial seizures. Apart from features of Sß^{O}-thalassemia, other hematologic investigations revealed normal results. These included ESR, PT and APTT. Serological tests were negative for brucella, hepatitis A, B and C, and human immunodeficiency virus (HIV) antibodies. At the age of 12½ years, he had MRI and MRA. These showed bilateral loss of brain parenchymal tissue noted in the territory of the middle cerebral arteries (MCAs) and to a lesser extent in that of the anterior cerebral arteries (ACAs). There was also high signal intensity and thinning bilaterally in the subcortical white matter, noted on T2-weighted and fluid-attenuated inversion recovery (FLAIR) images, indicating ischemic changes. Brain MRA revealed bilateral obliteration and occlusion of both internal carotid arteries (ICAs) at the level of the suprasellar region with no flow noted in either the MCA or anterior cerebral artery (ACA), bilaterally. The posterior cerebral artery was normal with several collaterals indicating moyamoya disease. There was also remarkable thickening of the calvarium indicating chronic anemia. The patient was maintained on aspirin, carbamazepine, and hydroxyurea.

Patient 5 (**Table 1**) was an 18-month-old girl who has been referred to the DPN due to floppiness, psychomotor delay, aphasia, and complex partial seizures. One month earlier, she sustained an episode of generalized seizures associated with aphasia and bilateral motor deficit. Reviewing her history, she was found to have been born with a scalp defect, which was oozing blood intermittently for a period of 7 months. This has been taken care of by the Division of Plastic Surgery of KKUH. Skull x-ray (**Figure 2a**) revealed soft tissue defect over the vertex with areas of bony defect in the underlying calvarium. Cranial CT scan (**Figure 2b**) delineated the areas of bony defect in the calvarium. There were no calcifications or ventricular enlargement. Electroencephalography showed epileptiform activity in the anterior regions mainly on the left side. She was started on carbamazepine. At the age of 26 months, repeated EEG showed multifocal spikes, polyspikes and slow waves of short duration (<1 minute) with no clinical manifestations. Brain MRI, at the aged of 36 months (**Figure 3**), showed generalized brain atrophy with wide sulci and dilated ventricles. There was cortical and subcortical encephalomalacia at the level of temporal and both occipital lobes associated with high signal intensity lesions on T2-weighted image on the left frontal and left parietal

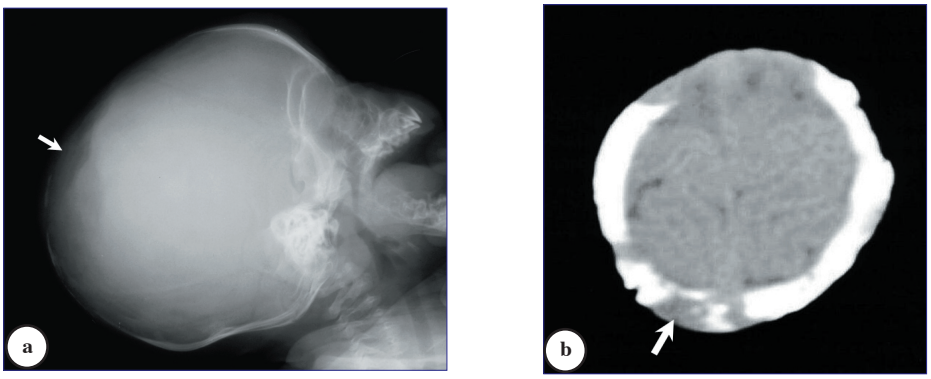

Figure 2 - **a)** Skull radiograph showing calvarial defect over the vertex (arrow). **b)** Cranial CT scan delineating the skull defect (arrow).

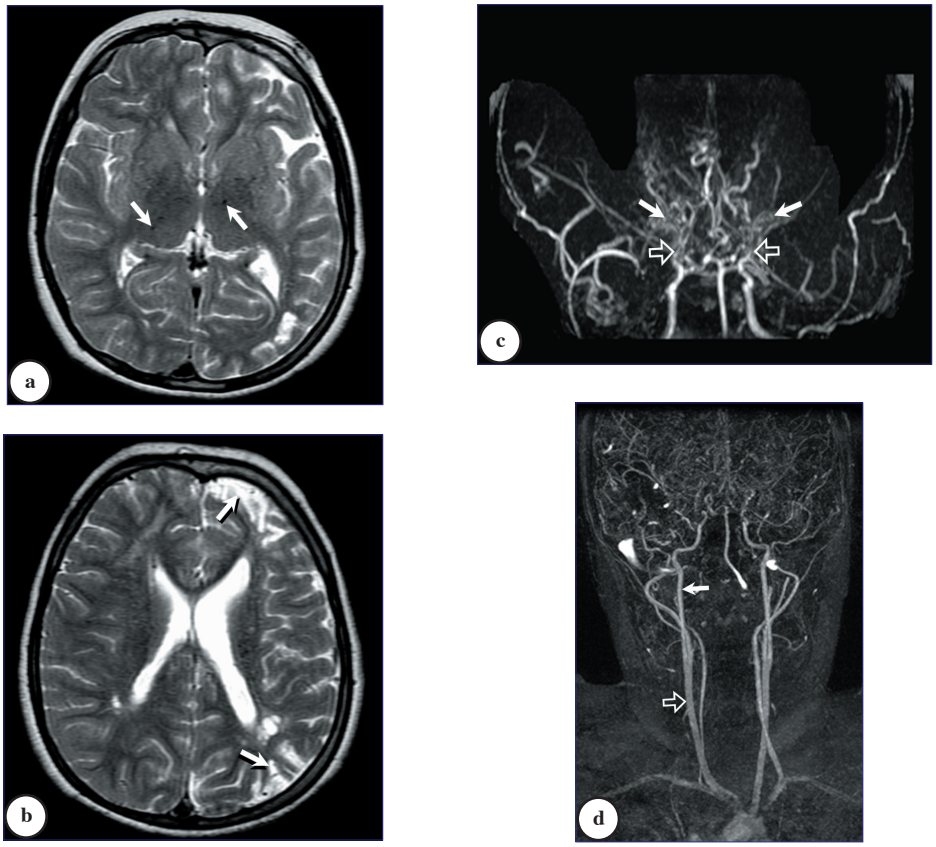

Figure 3 - **a)** Axial T2-weighted image of the brain showing multiple signal void foci in the basal ganglia (arrows) due to enlarged thalamoperforate collaterals. **b)** Axial T2-weighted image of the brain showing multiple high signal intensity lesions at the left frontal and left parietal cortex (arrows) and in the white matter adjacent to the trigone of both lateral ventricles due to old infarctions. **c)** MR angiography showing occlusion of both internal carotid arteries at the distal supraclinoid segment (open arrows) with dilated thalamoperforate collaterals (arrows). **d)** MR angiography of the neck vessels showing normal caliber of the common carotid (open arrow) and cervical part of the internal carotid arteries (arrow).

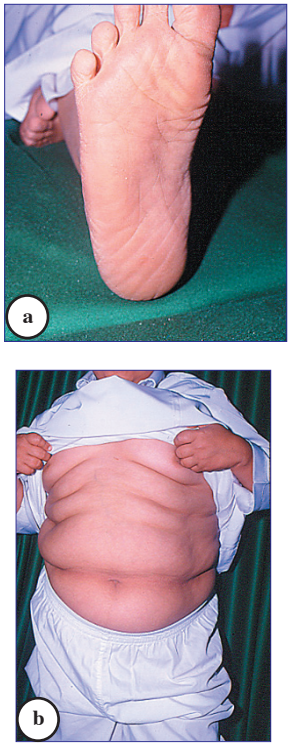

Figure 4 - Wrinkled skin is seen in **a)** the foot and, **b)** abdomen.

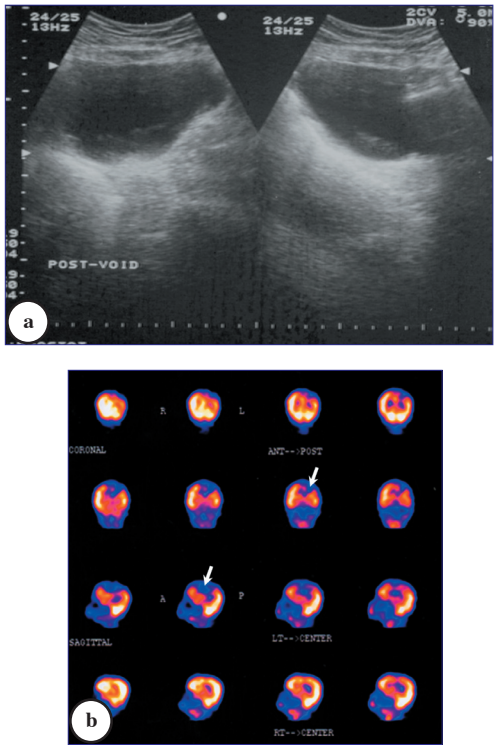

Figure 5 - **a)** Post voiding ultrasound examination of the pelvis showing distended urinary bladder. **b)** Brain SPECT showing perfusion defect in the left parietal lobe (arrows).

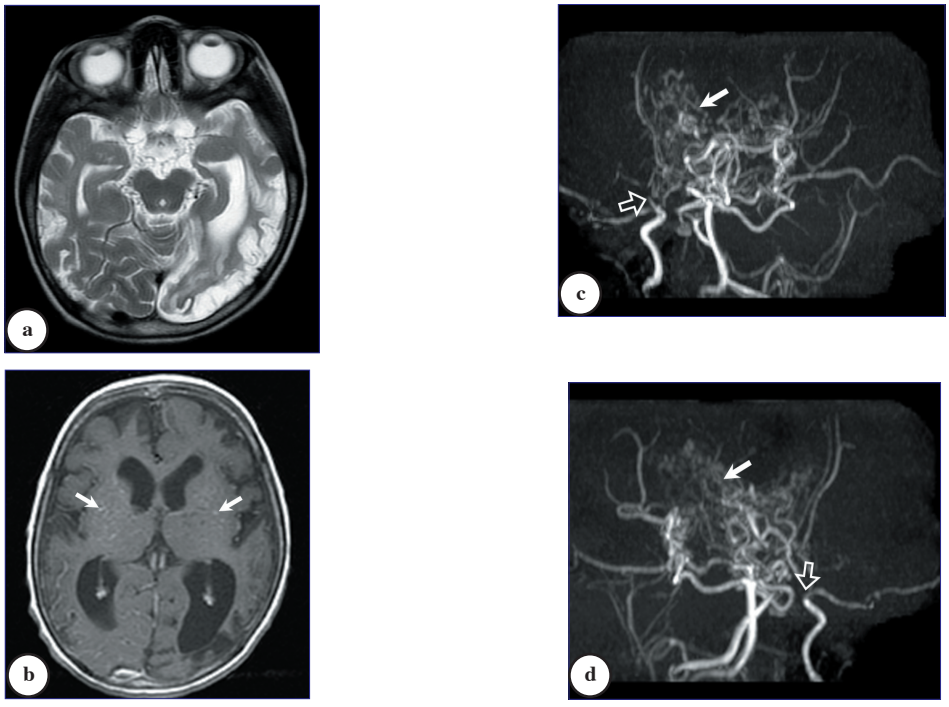

Figure 6 - **a)** Axial T2-weighted image of the brain showing left temporo-occipital cortical high signal due to infarction and multiple signal voids due to dilated collaterals in the basal cisterns. **b)** Enhanced axial T1-weighted image showing enhanced dilated basal collateral channels (arrows). **c & d)** MR angiography showing severely attenuated caliber of distal parts of both internal carotid arteries (open arrows), dilated collaterals (solid arrows), and normal caliber of posterior cerebral arteries.

cortex; features of old infarcts. Brain MRA (**Figure 3**) revealed narrowing of the supraclinoid portion of both ICAs and also both posterior cerebral arteries. There were prominent thalamostriate collaterals. Conventional four-vessel cerebral angiography showed typical moyamoya vessels associated with abnormal branches of the external carotid arteries (ECAs). There was severe bilateral narrowing of the ICA at the level of supra sellar cistern. The origin of both MCAs and ACAs were not defined. There was also narrowing of the right and left posterior cerebral arteries at P1 segment, absence of superficial temporal artery on both sides, and paucity of arteries in the frontoparietal region. Over several months, she had features of iron deficiency anemia for which she received treatment. At the age of 35 months, her Hb was 88 g/L (N = 105-135), MCV 56.1 fl (N = 77-85), MCH 17.6 pg (N = 23-31), RDW 18.1% (N = 11.5-14.5) and platelet count 777 x 10^9/L (N = 140-450). Coagulation and serological studies showed normal PT, APTT and anticardiolipin antibodies (ACLA). When aged 40 months, protein S assay revealed slightly reduced level of 72% (N = 80-140%) whereas protein C (84%) and antithrombin III (138%) were normal. At the age of 31 months, she underwent revascularization surgery in the form of EDAS and remained stable thereafter. Her dysmorphic features were re-evaluated at the age of 4 years and 4 months and were found to fit AOS. She was mentally retarded and microcephalic (skull circumference 43.5 cm <2 SD). She had aplasia cutis congenita on the vertex, and extending to the parietal region, mainly on the right side. There was cutis marmoratus in the upper and lower limbs, short fingers with hypoplastic nails (mainly the index fingers), syndactyly of the second and third toes bilaterally and several small toenails. In addition, she showed prominent mirror image movement, mainly of the hands and fingers.

Patient 6 (**Table 1**) was a 4-year-old boy who was evaluated at the DPN due to right-sided hemiparesis associated with right facial weakness. Two months earlier, he presented to a regional hospital with focal seizures and right-sided weakness dating back to one day prior to admission. His family gave a history of a previous episode of generalized seizures, which happened 7 days earlier, resulting in trauma to the occipital region of scalp and requiring stitching. Cranial CT scan was reported to show multiple infarctions of various sizes in both hemispheres. The largest of them was in the left frontal region. A diagnosis of "cerebrovascular accident" was made; he was hospitalized for 7 days, and was discharged in good general condition. His past medical history revealed the presence of hypotonia since birth, bilateral undescended testicles, and atrial septal defect, which closed spontaneously. There was also a family history of skin laxity, diagnosed as cutis laxa, in his older brother and 2 of his paternal cousins. On examination, and apart from the right facial weakness and hemiparesis, he had several dysmorphic features reminiscent of the WSS phenotype. These consisted of mid-face hypoplasia (excluding the malar region), hypertelorism, low-set ears, premature aging, high arched palate, and relative brachycephaly. His skin was wrinkled over the dorsum of the hands, feet, and abdomen (**Figure 4**). Veins were prominent over the hands. He had normal visual acuity and centiles for height and skull circumference. However, he had hyperextensible joints involving the hands and both elbows. Cranial CT scan showed a lacunar infarct at the posterior part of the left periventricular area and old ischemic changes in left frontal and occipital lobes. Brain MRI revealed several small rounded cystic changes in the peritrigonal white matter bilaterally, more pronounced on the left side. Hyperintense signal abnormalities were seen on T2-weighted images in the left frontal, left temporal and left parieto-occipital lobes in the watershed distribution. Cortical and subcortical hyperintensity was also seen in the right frontal lobe. There were numerous small abnormally appearing vessels, around the circle of Willis, in the basal ganglia, which were more prominent on the left side and suggestive of moyamoya disease. Hematologic investigations included CBC, which revealed features of hypochromic microcytic anemia with Hb 96 g/L (N = 120-140), MCV 62.1 fl (N = 77-85), MCH 17.9 pg (N = 23-31), and RDW of 17.9% (N = 11.5-14.5). Platelet count was normal at 385 x 10^9/L. Both PT and APTT were normal. However, 5 months after the presenting stroke, he had low protein C of 55% (N = 70-80%) and normal protein S (87%) and antithrombin III (100%). Repeated assay of these natural anticoagulants, carried out 5 years later, revealed normal results. Other investigations, which were normal or negative, included ACLA, serum brucella antibodies, serum amino acid profile, ECG, and echocardiography. Brain auditory evoked potentials were normal in the left ear and revealed features of sensorineural hearing loss in the right ear. Skeletal survey showed mild generalized reduction of bone density and no evidence of hip dislocation. Bone scan depicted symmetrical radiotracer uptake throughout the skeleton with no focus of abnormal uptake. Bone mineral density study of the lumbar spine and femoral neck revealed mild osteopenia. Abdominal ultrasound (**Figure 5a**) showed normal kidneys, but grossly distended bladder (up to the umbilicus) with large residue even after voiding.

Micturating cystourethrogram showed slightly irregular outline of the full bladder particularly superoposteriorly. The bladder wall irregularity became exaggerated during the micturating films. There was no evidence of vesico-ureteric reflux. The patient was referred to the Division of Neurosurgery for further management. However, his family declined any further invasive interventions. During the following 6 years from the initial stroke, he remained stable with mild residual right hemiparesis but declining school performance. Brain SPECT (**Figure 5b**) at the age of 10 years showed perfusion defect involving the left parietal lobe. Cranial MRI (**Figure 6**) revealed a large area of old infarct in the cortical aspect of the left frontal, parietal and temporo-occipital lobes; and few foci of cystic changes in the peritrigonal area bilaterally. The periventricular and subcortical white matter showed confluent areas of bright signal intensity on T2-weighted images and FLAIR sequence representing sequelae of ischemic changes. There were features of innumerable moyamoya vessels in the region of the basal ganglia bilaterally. Magnetic resonance angiography (MRA) showed normal neck vessels. There were, however, severe occlusive changes of the ICA at the level of the circle of Willis, the proximal part of the MCA and ACA bilaterally (**Figures 6c & 6d**). Diffuse attenuation of the caliber of the intracerebral part of both ICAs was also observed.

Discussion. Moyamoya syndrome remains rare in populations other than Japanese, Korean, and Chinese.[5,9] One of the cases included in this cohort (Patient 1, **Table 1**) was the first to be reported in the Arab ethnic group.[15] The disorder can be idiopathic or associated with acquired vasculopathies and genetic syndromes.[5,6,18] It is predominant in females and may occur at any age, but has 2 periods of relatively high incidence between the ages of 0 and 5 years and during the fourth decade.[1] The 6 cases described in this cohort revealed findings similar to those reported in the literature[1] since the female to male ratio was 2:1 and the first episode of stroke occurred at a mean age of 45 months (median 44 months). They also featured the typical presentation of the disease, namely, transient ischemic attacks or recurrent episodes of sudden hemiplegia, or both.[3] Other clinical presentations of MMS include motor and speech disturbances, cognitive decline, recurrent headaches and convulsions; all of which were present in various combinations in our cases. In contrast, adults commonly present with intracranial hemorrhage.[5,19] All of the 6 patients in our series had MMS associated with other diseases. Protein C deficiency was found in one patient and protein S deficiency in another. Two patients had associated hemoglobinopathies: SCD and Sß^{O}-thalassemia. Apart from these 2 patients who were not tested, results of ACLA were negative in the other 4 children. A fifth child had AOS associated with marginally low protein S, detected 9 months after revascularization surgery. This could not be confirmed later since the child did not avail for the test. However, the sixth patient had features of WSS phenotype and low protein C, detected 5 months after onset of stroke, which normalized later. We speculate that the latter 2 patients seem to have had transient deficiencies of these natural anticoagulants in the evolution of stroke and following surgery. It has been recommended to screen for prothrombic defects 3-6 months after the acute stroke onset.[20]

Few reports have described the association between prothrombic abnormalities and MMS.[19] Patient 1 (**Table 1**) in this series was the first reported case of MMS in association with deficiency of one of the natural anticoagulants, namely, protein C.[15] Apart from the typical intracranial angiographic features of moyamoya disease, she had extensive extracranial involvement, including the ECA and segmental involvement of the vertebral artery in its upper cervical region, suggesting a systemic vascular pathology in MMS.[16] Following this, other reports documented the association of MMS with either protein C or protein S deficiencies.[21-24] Based on these findings, recommendations were made that an evaluation of thrombophilia should be performed when both diagnosing and treating suspected cases of moyamoya disease.[22] However, the presence of acquired antiphospholipid antibodies, including ACLA and lupus anticoagulant in patients with MMS have been observed in several studies.[23-26] The origin of these antibodies and their role in the pathogenesis of MMS is still unclear.[19] It is noteworthy that none of the 4 patients tested in this study had raised ACLA. Two patients in the current series had MMS associated with SCD and Sß^{O}-thalassemia. This association was first described in children with SCD in 1972;[27] and its prevalence has recently been reported to be as high as 43% in SCD patients who had suffered strokes, while under the age of 18 years, despite their placement on chronic transfusions after stroke.[28] The new strategy of screening with transcranial Doppler (TCD) is likely to detect such cases early before the establishment of advanced cerebrovascular disease. Children with abnormal results on TCD should have neuroimaging with MRI, as the risk of stroke in children who have abnormalities in both TCD ultrasonography and MRI is higher than those with TCD abnormality alone.[29] Children with both abnormalities should strongly be considered for prophylactic transfusion therapy.

The 2 patients who had moyamoya phenomena associated with cutaneous syndromes deserve special emphasis. One of these was an 18-month-old girl who required revascularization surgery (EDAS) at the age of 31 months for angiographically documented MMS. She was born with a congenital scalp defect (associated with an underlying defect of the cranium); and was microcephalic and mentally retarded. She had cutis marmorata, short fingers with hypoplastic nails and several small toenails. These dysmorphic features fit the syndrome of AOS, which is characterized by the presence of a congenital scalp defect (scalp aplasia cutis congenita) associated with variable limb defects. The limb defects can range from absence of lower extremities below the mid-calf region to hypoplastic fingers, toes or nails.[30-32] Central nervous system anomalies, presenting as microcephaly, hemiplegia, epilepsy and mental retardation have been described in cases of AOS.[33,34] It is inherited as autosomal dominant with variable expressivity;[35] but can also be inherited as autosomal recessive.[31,36,37] Another prominent feature of the syndrome is the presence of cutis marmorata, described as cutis marmorata telangiectasia congenita.[38] The presence of cutis marmorata and its association with pulmonary hypertension, pulmonary arteriovenous malformation, congenital cardiac defects, and portal hypertension in some cases lead to the hypothesis that a congenital vascular abnormality is the underlying pathogenesis and that the cutaneous defects characteristically seen in AOS represents the most common manifestations.[38-40] This might offer an explanation to the finding, at such an early age, of MMS in our patient with AOS. Another risk factor for stroke in this patient was the recurrent scalp bleeding leading to iron deficiency anemia and thrombocytosis.[41] The other child was a 4-year-old boy who had MMS associated with WSS phenotype. He showed cutaneous features compatible with the syndrome including wrinkled skin over the dorsum of hands, feet, abdomen, palms and soles.[42] The venous pattern was prominent over the hands. It is noteworthy that following the initial paper of Gazit et al,[42] Karrar et al[43] described the WSS in 2 Saudi Arabian siblings, a brother and sister whose parents were first cousins, suggesting an autosomal recessive inheritance. Our patient had a family history of skin laxity, diagnosed as cutis laxa, in his older brother and 2 female paternal cousins. Elastic fiber abnormalities have been described in cases of WSS.[44-46] However, an increase in elastin accumulation in the thickened intima and increased elastin gene expression in arterial smooth muscle cells was described in patients with moyamoya disease.[47] This might suggest a role of elastin abnormalities manifesting as MMS in patients with WSS. The association between these 2 syndromes has not, hitherto, been reported.

Three of the 6 patients had revascularization surgery in the form of EDAS. The associated diseases in these 3 cases were protein C deficiency, SCD and AOS. The procedure and anesthetic consideration for the patient who had protein C deficiency have been described previously.[17] It is noteworthy that the potential benefits of successful revascularization surgery were established in many reports. It improves outcome, decreases stroke risk over time, affects angiogenesis, decreases the risk of future hemorrhage and prevents the gradual cognitive decline.[19,48-51] Its safety and efficacy have recently been reported in patients with SCD who develop MMS.[52] However, the optimal indications and timing of surgical revascularization in patients with MMS still await standardization.[12]

Aspirin is frequently used for secondary stroke prevention in children with MMS.[19,24] However, there is concern regarding using other more powerful agents (for example, oral anticoagulants) when recurrent ischemic events are not prevented by aspirin. Reasons for this are fear of subsequent subarachnoid hemorrhage, and as transient ischemic attacks in MMS seem to be provoked by vasospasm secondary to hyperventilation rather than due to a thromboembolic phenomenon.[17,19,53]

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