Infectious and inflammatory disorders of the circulatory system as risk factors for stroke in Saudi children

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ABSTRACT

Objective: To report on the role of infectious and inflammatory disorders as risk factors for stroke in a prospective and retrospective cohort of Saudi children.

Methods: Children, who presented with stroke, 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 periods July 1992 to February 2001 (retrospective study) and February 2001 to March 2003 (prospective study). Investigations for suspected cases included hemostatic assays, microbiological and serological tests. Neuroimaging included cranial CT, MRI, magnetic resonance angiography (MRA), magnetic resonance venography (MRV) and single photon emission computed tomography (SPECT) brain scan.

Results: Of the 104 Saudi children with stroke, seen during the combined study periods of 10 years and 7 months, infectious and inflammatory disorders of the circulatory system were the identified risk factor in 18 (17.3%). Five children had stroke following acute bacterial meningitis at ages ranging between 5-21 months. The causative organism was identified in 3 of them and consisted of *Haemophilus influenzae* (in a 5-month-old girl), *Streptococcus pneumoniae* (in a 21-month-old girl complicated by subdural empyema and sinovenous thrombosis), and *Staphylococcus aureus* in a 6-month-old boy who had an underlying chronic granulomatous disease. Unspecified meningitis/meningoencephalitis affected 4 patients, whereas 3 children had an underlying congenital infection as a cause for their stroke. Two of the latter 3 children were diagnosed to have congenital toxoplasmosis, and the third had congenital rubella syndrome. Two girls had stroke following septicemia at ages of one and 2 months. Neurobrucellosis caused stroke in 2 boys at the ages of 4½ and 4 years. In both patients, neuroimaging revealed lacunar and other infarcts involving mainly the deep cerebral nuclei, secondary to occlusion of small penetrating end arteries. Two patients presented with cerebrovascular disease following systemic lupus erythematosus. These were a 12-year-old girl and a 5-year-old boy.

Conclusions: Several of the infectious diseases that caused stroke in this cohort of Saudi children are potentially preventable through childhood immunization programs or other maternity health programs. In particular, immunogenic conjugate vaccines against the 3 most common organisms causing acute bacterial meningitis (*Haemophilus influenzae* type b, *Neisseria meningitidis* and defined serotypes of *Streptococcus pneumoniae*) are needed to protect the young (<2 years) who are mostly affected.

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Acute infections of the central nervous system (CNS) or the meninges may lead to stroke in children. The most important of these is acute bacterial meningitis,[1-4] which has recently become

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amenable to prevention through childhood immunizations programs.[5] They also include acquired immunodeficiency syndrome through both infectious and non-infectious mechanisms.[6,7] Infections outside the CNS may also predispose to cerebral infarction. Childhood head and neck infection and exanthematous diseases were reported to be associated with stroke.[8-11] Sinovenous thrombosis is typically encountered following head and neck infections such as otitis media, sinusitis and mastoiditis.[12] An association of idiopathic childhood infarction (following viral infections) with HLA-B51 has been reported.[13] Stroke following recent infection with *Mycoplasma pneumoniae* is well-recognized.[14] Other reported associations include influenzae A virus,[15] entroviral,[16] parovirus B19 infections[17] and neuroborreliosis.[18] Also varicella is increasingly recognized as a cause of acute ischemic events following primary chickenpox infection in childhood.[19-21] Varicella-associated stroke results from cerebral vasculitis and can prove to be fatal.[22,23] Non-infectious inflammatory diseases, secondary to an associated vasculitis in the cerebral vessels may cause stroke in children. These include systemic lupus erythematosus (SLE), Kawasaki disease, polyarteritis nodosa, Takayasu disease, mixed connective tissue disease, rheumatoid arthritis, dermatomyositis, inflammatory bowel diseases, and primary or isolated angiitis of the central nervous system.[24,25] It is noteworthy that hematological abnormalities contribute significantly to the pathogenesis of stroke in these autoimmune diseases secondary to the development of an antiphospholipid antibody syndrome.[26] The presence of antiphospholipid antibodies increases, by itself, the risk for arterial and venous thrombosis in children, and 50% of these occur in the CNS.[27] The present study describes the clinical, neuroimaging and laboratory features of stroke due to infectious and inflammatory disorders in a prospective and retrospective cohort of Saudi children.

Methods. The study includes a cohort of 104 Saudi children, 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 continued for 8 years and 7 months (July 1992 to February 2001). Relevant information regarding each affected child was retrieved in a specially designed comprehensive protocol including the pertinent clinical, neuroimaging, neurophysiological and laboratory data. Details of these, as well as the laboratory methods are found elsewhere.[28-30]

Results. Infectious and inflammatory disorders of the circulatory system accounted for stroke in 18 (17.1%) of 104 children (aged 1 month to 12 years). Infectious disorders included acute bacterial meningitis in 5 (4.8%) cases, meningitis/meningoencephalitis (unspecified) in 4 (3.8%), congenital infections in 3 (2.9%), septicemia in 2 (1.9%), and neurobrucellosis in another 2 (1.9%) children. On the other hand, inflammatory diseases, in the form of SLE, resulted in stroke in 2 (1.9%) patients. A summary of the clinical and neuroimaging features of these cases is depicted in **Table 1**. Five children had stroke following acute bacterial meningitis at ages ranging between 5-21 months (**Table 1**). The organism was identified in 3 of them and consisted of *Haemophilus influenzae* (*H. influenzae*), *Streptococcus pneumoniae* (*S. pneumonia*), and *Staphylococcus aureus* (*S. aureus*).

Meningitis due to *S. pneumonia* inflicted a 21-month-old girl (**Table 1**, Patient 2), and was complicated by left frontal cerebral hemisphere infarct, subdural empyema, and thrombosis of the posterior segment of the sagittal sinus, right transverse and straight sinuses (**Figure 1**). Hematologic investigations, in this patient, showed high erythrocyte sedimentation rate (ESR) of 95 mm/hr and raised fibrinogen (8.6 g/L; N = 2-4 g/L). Other investigations that revealed normal or negative results included complete blood count (CBC), prothrombin time (PT), activated partial thromboplastin time (APTT), protein C, protein S, antithrombin III, antinuclear antibodies (ANA), anticardiolipin antibodies (ACA), serum brucella titre and mycoplasma IgM antibodies.

A 6-month-old-boy (**Table 1**, Patient 3) presented with seizures, drowsiness, and lethargy and gave history of periorbital cellulites. Investigations revealed turbid cloudy cerebrospinal fluid (CSF), which grew *S. aureus*. Blood culture was also positive for the same organism. Complete blood count showed polymorphonuclear leucocytosis (WBC = 27.9 x 10^9/L) and features of hypochromic microcytic anemia (Hb = 107 g/L). Cranial CT, 2 days after the onset of symptoms, showed a right frontal hypodense area with peripheral enhancement. A repeat CT at 10 days depicted features of right frontal lobe hemorrhagic infarct. Echocardiography revealed mild tricuspid regurgitation and no other vascular abnormality. Assay of phagocytic function showed decreased respiratory burst response in the patient's whole blood when stimulated with both phorbol myristate acetate (PMA) and opsonized zymosan (OPZ), thus confirming the underlying chronic granulomatous disease in this

Table 1 - Clinical characteristics of patients with infectious and inflammatory disorders of the circulatory system.

Patient	Gender	Age at onset/ diagnosis (years)	Age when evaluated at DPN (years)	Site and type of stroke (CT/MRI findings)	Underlying infection/ inflammatory disorder	Other complications, associated findings and sequelae	Duration of follow-up (years)	Outcome
1	F	0.4	4	Multiple lacunar supratentorial infarcts, brain atrophy	*Haemophilus influenzae* meningitis	Right hemiparesis, neurodevelopmental delay, epilepsy, bilateral optic pathway involvement on VEP	1.3	Alive
2	F	1.8	2.2	Left frontal infarct, sinovenous thrombosis	*Streptococcus pneumoniae* meningitis	Subdural empyema, left hemiparesis, left facial nerve palsy, dysphasia/poor speech, cognitive deficits	0.2	Alive
3	M	0.5	0.5	Right frontal lobe hemorrhagic infarct	*Staphylococcus aureus* meningitis	Chronic granulomatous disease, mild tricuspid regurgitation, delayed language development, epilepsy	1.7	Alive
4	M	0.6	4.9	Left MCA infarct	Bacterial meningitis	Right hemiparesis, neurodevelopmental delay, epilepsy	1	Alive
5	F	0.5	2.5	Left frontotemporal infarct	Bacterial meningitis	Right hemiparesis, dysphasia/ poor speech, cognitive deficits, epilepsy	0.7	Alive
6	F	3	9	Right hemisphere porencephalic cyst	Unspecified meningitis/ encephalitis	Left hemiparesis, cognitive deficits, epilepsy	3.6	Alive
7	F	0.7	6.3	Left parietotemporal infarct (left MCA territory)	Unspecified meningitis/ encephalitis	Right hemiparesis/dystonia, epilepsy	7	Alive
8	F	0.6	3.8	Right hemisphere atrophy, lacunar infarcts involving left head of caudate and lentiform nuclei	Unspecified meningitis/ encephalitis	Bilateral motor deficits: left>right, dysphasia/poor speech, cognitive deficits, epilepsy	3.5	Alive
9	F	1	6.5	Bilateral frontoparietal ischemic changes, bilateral hippocampal sclerosis	Unspecified meningitis/ encephalitis	Dysphasia/poor speech, cognitive deficits, epilepsy	2.8	Alive
10	F	0.4	4.8	Left parietal lobe infarct, bilateral multifocal hemispheric infarcts, intracranial calcifications	Congenital toxoplasmosis	Poor coordination, dysphasia / poor speech, epilepsy	2.3	Alive
11	M	3 days	2	Left porencephalic cyst; periventricular, intraparenchymal and left orbital calcifications	Congenital toxoplasmosis	Left microphthalmia, hydrocephalus, right hemiparesis, neurodevelopmental delay, epilepsy	4.8	Alive
12	M	0.3	9	Right hemisphere, brain stem and cerebellar atrophy; right parietal schizencephalic defect with calcifications. MRA showed paucity of vessels in the right side	Congenital rubella syndrome	Sickle cell trait, left hemiparesis, cognitive deficits, epilepsy	7.8	Alive
13	F	0.1	9	Right frontal porencephalic cyst, right temporoparietal ischemic changes	Septicemia	Left hemiparesis, left facial nerve palsy, dysphasia/poor speech, cognitive deficits	7.5	Alive
14	F	0.2	0.2	Diffuse atrophic brain changes, bilateral fronto-parietal subdural hematomas	Septicemia	DIC shock, spastic quadriplegia, neurodevelopmental delay, epilepsy	1.3	Alive
15	M	4	4	Lacunar infarcts at right basal ganglia and right frontal lobe. Ischemic changes in right Sylvian fissure and posterior parietal region	Neurobrucellosis	Left hemiparesis, left facial nerve palsy	1.3	Alive
16	M	4.5	4.5	Ischemic changes in the genu, posterior limb of right internal capsule, right cerebral peduncle and right hypothalamus	Neurobrucellosis	Left hemiparesis, left facial nerve palsy, dysphasia/poor speech	1.7	Alive
17	F	12	12	Bilateral frontal and left cerebellar arterial ischemic changes	Systemic lupus erythematosus	Left hemiparesis, recurrent headaches, epilepsy	6.7	Alive
18	M	5	5.3	Chronic subdural collection (hygroma), generalized cortical brain atrophy	Systemic lupus erythematosus	Spastic quadriparesis, aphasia, cognitive deficits	Lost to follow-up	Alive

DPN - Division of Pediatric Neurology, VEP - visual evoked potentials, MCA - middle cerebral artery, MRA - magnetic resonance angiography, DIC - disseminated intravascular coagulation

patient. Following therapy, he recovered with no motor deficits but had delayed speech and residual partial epilepsy.

Unspecified meningitis/meningoencephalitis. Four girls (**Table 1**, Patients 6-9), who had history of stroke following a febrile illness, were evaluated at ages ranging between 45 months and 9 years. The stroke episodes happened at ages ranging between 7 months and 3 years. They were characterized, apart from fever, with irritability or coma, and were associated in 3 patients with hemiplegia or bilateral motor deficit. An episode of seizure was also a presenting symptom in 3 of them. The diagnosis of unspecified meningitis/encephalitis was offered to account for the febrile episode in each case. Radiological investigations, including cranial CT and MRI, revealed features of cerebral ischemic insults. These included right porencephalic cyst in one patient, infarction in the distribution of the left middle cerebral artery (MCA) territory in another; and right cerebral hemisphere atrophy associated with lacunar infarcts, involving the left head of caudate and lentiform nuclei, in the third. The fourth patient had bilateral hippocampal sclerosis (more severe on the right) associated with bilateral fronto-parietal subcortical white matter lesions suggestive of ischemic changes.

Congenital infections. Three children (**Table 1**, Patients 10-12) had an underlying congenital infection as a cause for their stroke. These consisted of 2 who had congenital toxoplasmosis and one who had congenital rubella syndrome. The first patient with congenital toxoplasmosis (**Table 1**, Patient 10) was evaluated at the DPN at the age of 4 years and 9 months. Her symptoms started with seizures at the age of 5 months followed by psychomotor delay. Physical examination revealed height and weight below the 5th centile for age and skull circumference at 2 SD below the mean. Cranial CT showed multiple intracerebral calcifications at both the periventricular area and the grey/white matter junction. Brain MRI, at the age of 5 years, depicted a small wedge-shaped infarct at the left parietal lobe associated with non-enhancing bilateral multifocal hemispheric infarcts. Functional imaging using single photon emission computed tomography (SPECT) brain scan revealed reduced regional cerebral blood flow in the left parietal lobe. Screening of toxoplasma[31] at the age of 4 years and 9 months was positive for IgG and negative for IgM antibodies. Similar results were obtained for her mother.

The second child (**Table 1**, Patient 11) presented to the DPN at the age of 2 years with psychomotor delay, complex partial seizures, mild generalized spasticity, and right-sided hemiparesis. He had a history of right-sided focal seizures with secondary generalization on the third day of life. Cranial CT, at 8 days of age, demonstrated obstruction of the aqueduct of Sylvius and dilatation of the third and lateral ventricles. The left lateral ventricle was most severely affected. Dense, large calcifications were seen in the basal ganglia and were associated with multiple periventricular calcifications. Screening for toxoplasma antibodies (using latex agglutination test) was positive in the patient and his mother. The titers were 1/1024 in the patient, and 1/256 in his mother. A diagnosis of congenital toxoplasmosis was made, and he received treatment for one year including prednisolone, pyrimethamine, sulphadiazine, and folinic acid. A ventriculoperitoneal shunt was also inserted at 2 months of age. On examination, he was found to be microcephalic and had microphthalmia of the left eye associated with cataract. The right eye showed the features of focal necrotizing retinitis as macular scar. He also had mild generalized spasticity and right-sided hemiparesis. A repeat CT brain at the age of 5 years showed the ventriculoperitoneal shunt to be in position in the right lateral ventricle. There was a large CSF fluid-filled structure on the left side in continuity with the temporal horn of the left lateral ventricle, interpreted as a possible parencephalic cyst communicating with the left lateral ventricle. There was no gross midline shift but periventricular, intraparenchymal, and left orbital calcifications.

Another 9-year-old boy (**Table 1**, Patient 12) who was evaluated due to left-sided hemiparesis, cognitive deficits, and complex partial seizure had a history of congenital rubella syndrome. He has been diagnosed at the age of 3 months following the presence of rubella-specific IgM antibodies and cerebral calcifications on cranial CT scan, which also revealed a right-sided calcified schizencephalic defect with smooth thick gyri (speckled with calcifications) involving the parietal region. Investigations, at the age of 9 years, showed normal CBC, ESR, PT, APTT, serum amino acids and urine organic acid profile. However, Hb electrophoresis revealed the presence of sickle cell trait. Cranial MRI showed small size of the right cerebral hemisphere with prominence of the right lateral ventricular system. There were smooth thick gyri of the right cerebral hemisphere associated with small size of the right side of the brain stem and cerebellum. Magnetic resonance angiography (MRA) showed paucity of vessels on the right side.

Septicemia. Another 2 girls developed motor deficits following febrile illnesses compatible with septicemia at ages of one and 2 months. The first one (**Table 1**, Patient 13), who was evaluated at the DPN, at the age of 9 years, was reported to have had

septicemia at one month of age when she was admitted at a regional hospital with fever. She had residual left hemiparesis associated with left facial nerve palsy, poor speech, and cognitive deficits. Cranial CT and MRI revealed right frontal porencephalic cyst and features of right temporoparietal ischemic changes. The second girl (**Table 1**, Patient 14) was aged 2 months and presented one day after a febrile illness associated with vomiting, irritability, and seizures. This progressed to disseminated intravascular coagulation (DIC) and shock. Cranial CT and subsequent MRI showed moderate to marked atrophic brain changes and bilateral fronto-parietal subdural hematomas.

Neurobrucellosis. Stroke following neurobrucellosis was observed in 2 children. The first (**Table 1**, Patient 15) was a 4-year-old boy who presented 2 months earlier with fever, muscle aches, left knee arthritis and hepatomegaly. Following investigation at a hospital in the Southern Region, he was diagnosed to have brucellosis and was treated with "injections" for 2 weeks. There was history of drinking raw milk and 12 other family members were diagnosed to have brucellosis. However, 6 weeks after the initial symptoms, he had left-sided focal seizures associated with left-sided hemiplegia. Cranial CT was reported to show a large irregular low attenuation area in the right hemisphere not enhancing with contrast. When examined at KKUH, he had left facial palsy and left hemiparesis. The CSF examination showed 11 x 10^6 WBC/L, protein 0.15 g/L, glucose 2.9 mmol/L and Gram-negative coccobacilli on microscopy. Both blood and CSF cultures were negative for brucella. Complete blood count revealed microcytic hypochromic anemia (Hb = 109 g/L), whereas Hb electrophoresis was normal. The serum brucella antibody titre was significantly high for brucella abortus (1:320). Immunoglobulin profile was normal. Cranial MRI (**Figure 2**) showed a 2.5 cm x 1.5 cm lesion involving the right basal ganglia with low signal intensity on T1-weighted images and high signal intensity on T2-weighted images; likely representing a focus of encephalomalacia secondary to involvement of the striatal vessels. A similar lesion (5 x 5 mm) was seen lateral to the frontal horn of the right lateral ventricle. There were also areas of increased signal changes at the grey/white matter junction in the region of the Sylvian fissure and in the right posterior parietal region. These were interpreted to represent a small amount of blood or changes of vasculitis. Electrocardiography (ECG) and echocardiography were normal. He was treated with rifampicin and trimethoprim-sulphamethoxazole (TMP-SMX) for a period of 4 months. He maintained follow-up for another 11 months during which he remained well with no seizure disorder but residual left-sided hemiparesis associated with left facial nerve palsy.

The second child (**Table 1**, Patient 16) was a 4½-year-old boy who was admitted to KKUH 4 days after developing left-sided hemiparesis. He had been diagnosed to have brucellosis 3 months before admission and serological investigations showed remarkably high serum brucella antibody titre of 1:1421. He received gentamicin, rifampicin and TMP-SMX for 6 weeks. Follow-up brucella antibody assay revealed negative results. On examination, in addition to the hemiplegia, he had partial right occulomotor nerve palsy, upper motor neuron left facial nerve palsy and left cerebellar dysfunction. Plantar responses were extensor bilaterally. Initial hematological investigations showed Hb 69 g/L, WBC 2.4 x 10^9/L (lymphocytes 73% and neutrophils 23%), platelets 53 x 10^9/L, normal mean corpuscular hemoglobin, slightly low mean corpuscular volume (MCV, 77.8 ft; N = 80-91), ESR 20 mm/hr; and normal results for PT, APTT and D. Dimer. Results for ACA, Hb electrophoresis, lipid profile and serum amino acids were normal. Blood and CSF cultures for brucella were negative. Electrocardiography and echocardiography revealed normal results. Cranial MRI (**Figure 3**) showed a low signal intensity lesion in the right cerebral peduncle. This lesion appeared to be extending from the junction of the pons and mid brain to involve the right thalamus with mass effect on the 4th ventricle. There was no evidence of hydrocephalus. The lesion showed high signal intensity on fluid-attenuated inversion recovery (FLAIR) images and the central portions of it showed enhancement after Gadolinium injection with low signal intensity surrounding it. These signal changes involved the posterior limb of the right internal capsule. Normal flow-void was identified in the deep cerebral venous system. Chemotherapy for brucellosis was restarted (in the form of gentamicin, rifampicin and TMP-SMX) with other supportive treatments, as required. A repeat MRI, carried out 3 weeks later (**Figure 3d**), showed remarkable improvement with near complete resolution of the previously described lesions. However, there were small hyperintense foci in the genu and posterior limb of the right internal capsule, and the right cerebral peduncle seen on T2 and FLAIR images. Residual hyperintensity was noted in the right hypothalamus in the same sequences. Two months following the initial MRI, the lesions regressed completely.

Inflammatory diseases. Systemic lupus erythematosus. Two patients presented with cerebrovascular disease following SLE. The first

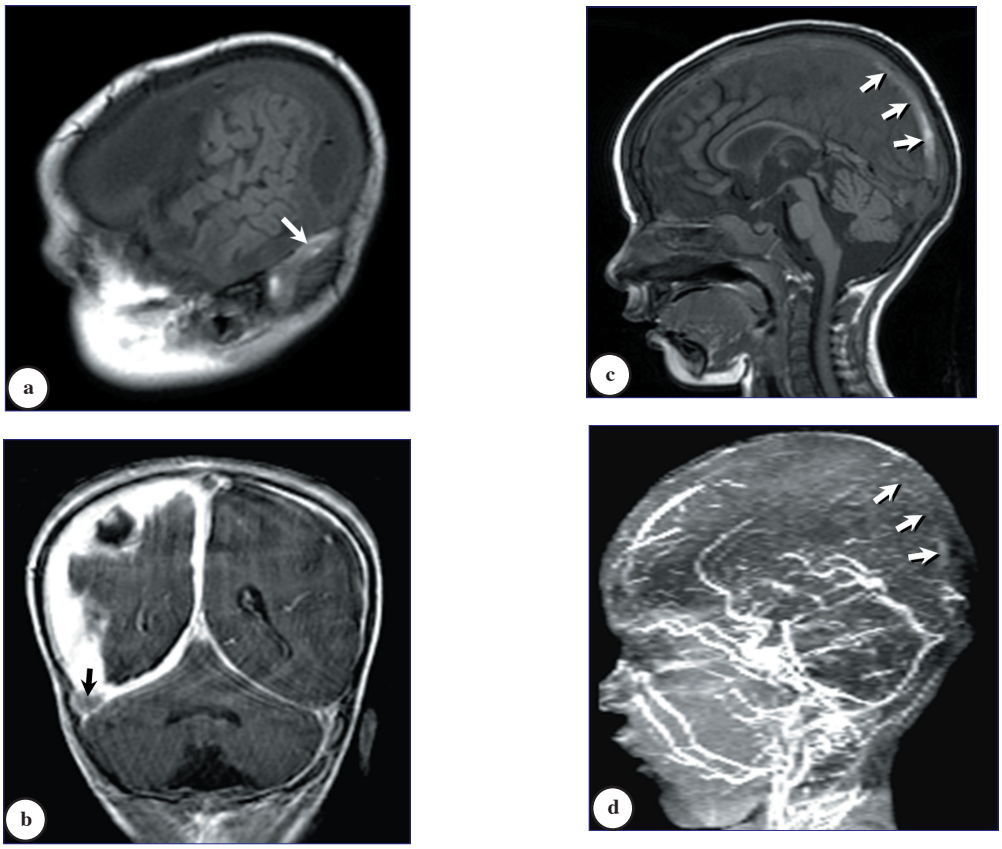

Figure 1 - a) Sagittal T1-weighted MR image of the brain showing curved band of high signal intensity within an expanded right lateral sinus (arrow) indicating thrombosis. Extensive subdural collection is seen surrounding the right cerebral hemisphere. **b)** Post-contrast coronal T1-weighted MR image showing thick and strongly enhancing dura including falx cerebri and tentorium cerebelli. The right lateral sinus is expanded and filled with large thrombus (arrow). **c)** Mid-sagittal T1-wieghted MR image of the brain showing curved band of high signal intensity in the superior sagittal sinus representing thrombosis (arrows). **d)** MR venogram study showing lack of flow within the superior sagittal sinus because of thrombosis (arrows).

(**Table 1**, Patient 17) was a 12-year-old girl who presented to KKUH 4 days after onset of headache, inability to move, excessive sleepiness and squint of the left eye. On examination, she had erythematous blush, mouth ulcers, cutaneous vasculitis of feet and hepatosplenomegaly. Neurological examination revealed obtunded sensorium associated with left third, sixth and seventh cranial nerve palsies; and left hemiparesis. She had been diagnosed to have SLE since the age of 10 years. Investigations revealed proteinuria (++), hemoglobinuria (++) and positive urine culture for *Escherichia coli*. She had a high ESR of 90 mm/hr but normal PT, APTT and fibrinogen. Antinuclear antibodies were positive (ranging between 1:320 and 1:1230), whereas anti-double-stranded DNA was negative. Both anti-SSA (881U) and anti-SSB (1072U) antibodies were positive. Serum levels of total hemolytic complement (CH50) were normal but C_3 and C_4 were decreased. Anticardiolipin antibodies were raised (IgG 18 GPL/ml; N = 6-12; IgM 12 MPL/ml, N = 6-11). Electrocardiography, echocardiography, EEG and cranial CT (with and without contrast) were all normal. Brain MRI showed bilateral frontal white matter hyperintense foci associated with left cerebellar atrophic changes, features attributed to ischemia following vasculitis. During a follow-up period of at least 6 years, she was left with residual left hemiparesis, and developed recurrent headaches and epilepsy (with generalized tonic-clonic seizures).

The second patient (**Table 1**, Patient 18) was a 5-year and 4 month-old-boy who presented to the DPN with a history of inability to move, irritability, generalized seizures and aphasia. He had presented 4 months earlier to a regional hospital one day after being unable to move. He also gave history of progressive

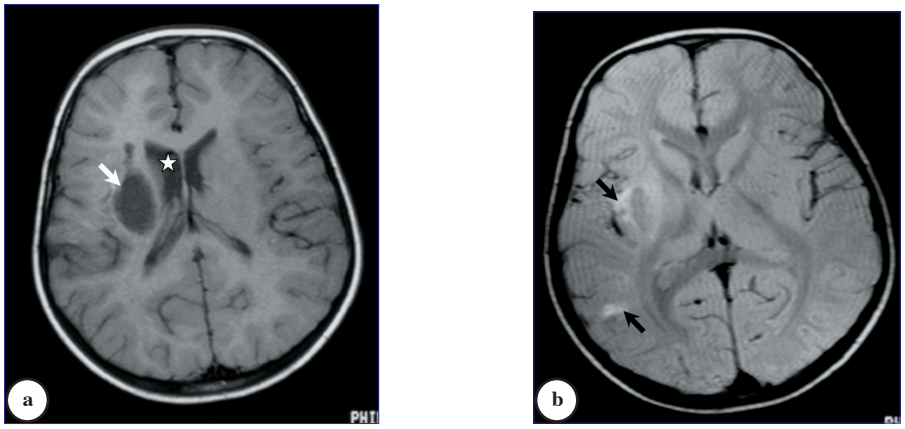

Figure 2 - **a)** Axial T1-weighted brain MR image showing hypointense lesion (cephalomalacia) in the right basal ganglia (white arrow) associated with ectasia of the adjacent right lateral ventricle (asterisk). **b)** Axial FLAIR image showing hyperintensity adjacent to the lesion and in the right parietal lobe (black arrows) due to gliosis.

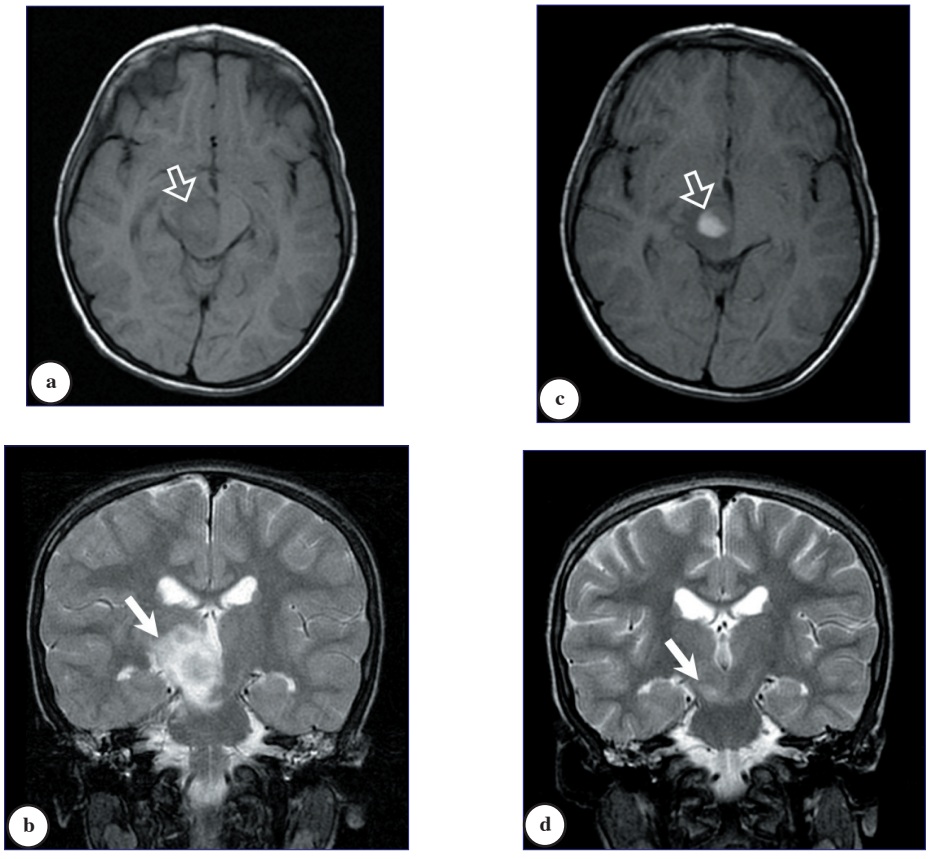

Figure 3 - **a)** Axial T1-weighted brain MR image showing a large low signal intensity lesion in the right side of the midbrain (open arrow). **b)** Coronal T2-weighted image showing the lesion extending to the right thalamus with high signal intensity (arrow). **c)** Enhanced axial T1-weighted image showing intense enhancement of the central part of the lesion (open arrow). **d)** Follow-up coronal T2-weighted image 3 weeks later showing remarkable improvement with near complete resolution of the lesion. A small residual high signal is seen (arrow).

loss of intellectual functions and milestones, as well as, recurrent convulsions since the age of 4 years. He was diagnosed at the regional hospital in the Eastern Province to have SLE based on the clinical features and positive ANA (1:640) on serology. He received pulse intravenous corticosteroid therapy for 3 days followed by oral prednisone (2 mg/kg/day), which has been tapered over 5 weeks. Investigations following admission to the regional hospital after the episode of motor weakness included EEG, which was reported as showing mild to moderate generalized non-specific disturbance of cerebral activity. Examination of CSF revealed WBC 35 x 10^6/L (10% neutrophils and 90% polymorphs), red blood cell 25 x 10^6/L, normal biochemistry and negative culture. When admitted to KKUH, Riyadh, he was found to be failing to thrive (both weight and height were below 5th centile for age). He had mouth ulcerations and photophobia. His hair was brittle, there were areas of alopecia, he was still aphasic and had spastic quadriplegia. Cranial CT showed chronic subdural collection (hygroma) and MRI also revealed generalized cortical brain atrophy. Hypochromic microcytic anemia was depicted on CBC (Hb 6.9 g/L), platelets were 229 x 10^9/L and ESR 25 mm/hr. Other investigations that showed negative or normal results were urine examination, blood culture, PT, APTT, ANA, anti-double-stranded DNA, LE cells, ACA, immunoglobulins, C3 and C4. Abnormal positive results included C-reactive protein, rheumatoid factor, and anti-Smith antibody. Anti-SSA antibody was positive whereas anti-SSB was negative.

Discussion. Stroke is known to complicate acute infections of the CNS or the meninges. The mechanism of ischemic injury in such situations includes direct inflammation of the blood vessels in the CNS or hematological disturbances causing hypercoagulable states. Other mechanisms include an associated systemic hypotension or the presence of cardiovascular disorders causing distant emboli.[25]

Acute bacterial meningitis. In the current study, 5 children had stroke following acute bacterial meningitis at ages ranging between 5-21 months. The 3 identified organisms were *H. influenzae*, *S. pneumoniae* and *S. aureus*. The latter organism caused a hemorrhagic infarct in an immunocompromised 6-month-old boy who had chronic granulomatous disease. Conversely, *H. influenzae* and *S. pneumoniae* are amongst the main bacteria that cause endemic childhood meningitis in both the developed and developing world.[1,32] Stroke following meningococcal disease (a well-known association) has not been seen in this series.[2] The disease occurs as both endemic and epidemic in most parts of the world, including Saudi Arabia.[1,32-35] Serogroups A, B and C account for approximately 90% of all cases worldwide.[1] Recently, serogroup W135 emerged in Saudi Arabia and lead to 2 major outbreaks mainly among Pilgrims during the Hajj season of 2000 and 2001.[36] The epidemic clone of serogroup W135, which caused the year 2000 global outbreak of meningococcal (MC) meningitis that began in Saudi Arabia, was later detected in pilgrims and their family contacts in Morocco, Oman and Sudan.[37] This signaled potential outbreaks in these countries. In Saudi Arabia, a study[38] covering the period from January 1999 to December 2002, observed increased proportion of cases of MC meningitis due to serogroup W135 (up to 95%). In this study, 32% of cases were children aged <2 years and 58% were <5 years of age. Invasive MC disease is potentially preventable by immunization with quadrivalent MC vaccines. Saudi children vaccinated with the quadrivalent polysaccharide MC vaccine (ACYW135), showed adequate response for serogroups A, C, Y and W135 of *Neisseria meningitidis (N. meningitidis)*, but after the age of 4 years.[39] It is noteworthy that bacterial polysaccharides, including those comprising the capsule of *N. meningitidis, H. influenzae* and *S. pneumoniae,* are T-cell-independent antigens. Conjugation of polysaccharides to a protein carrier that contains T-cell-independent epitopes, leads to an improved primary response to the polysaccharide and strong anamnestic response to re-exposure.[40] The rapid disappearance of *H. influenzae* type b was observed following routine childhood immunization with conjugate vaccines.[5,35] In the USA, conjugate *H. influenzae* type b and conjugate *S. pneumoniae* vaccines, were introduced for mass infant immunization in 1990 and 2000.[41] Both have been successful in reducing the incidence of disease caused by serotypes contained in the vaccines, and in decreasing asymptomatic carriage of the respective bacteria.[41] In a recent study from the UK,[42] a combined 9-valent pneumococcal-group C meningococcal conjugate vaccine (Pnc9-MenC), administered to infants, within the immunization schedule, at age 2, 3 and 4 months, was immunogenic for all contained pneumococcal serotypes. However, immunogenicity for MenC was reduced. Most recently, a tetravalent MC conjugate vaccine (A, C, Y, W135) has been recommended by the Advisory Committee on Immunization Practices[43] to be given routinely for young persons aged 11-12 years. Clinical trials are underway in the USA for the use of this vaccine in children 2-10 years and in infants.[44] With regards to Saudi children, and as has previously been recommended for those living in other parts

of this Region,[1] immunogenic vaccines against the most common organisms (*H. influenzae* type b, *N. meningitidis* and defined serotypes of *S. pneumoniae*) are still needed to cover the young (<2 years) who are mostly affected. It is noteworthy that the 21-month-old girl who had *S. pneumoniae* meningitis developed subdural empyema associated with cerebral venous thrombosis. Sinovenous thrombosis is known to complicate purulent meningitis and is typically found in the context of head and neck infections, dehydration and hypercoagulable hematologic disorders.[26] In this patient, a panel of investigations for hypercoagulability revealed negative results. Due to the increased venous pressure, venous infarctions resulting from cerebral sinovenous thrombosis can cause ischemic stroke with hemorrhagic conversion. This might explain the frontal lobe hemorrhagic infarct associated with *S. aureus* meningitis and preceded by periorbital cellulitis in the 6-month-old boy who had chronic granulomatous disease.

Unspecified meningitis/meningoencephalitis. Four children developed stroke following an unspecified episode of meningitis/encephalitis. The mechanism of ischemic injury in such cases results from local inflammation of the meninges extending to the intracranial blood vessels. Alternatively, impaired cerebral perfusion following intracranial hypertension increases the likelihood of ischemic lesions in the border zones of major arterial territories.[25] Meningoencephalitis complicated by stroke, has been described following infections with *Mycobacterium tuberculosis, Treponema pallidum, Mycoplasma pneumoniae*, HIV, Japanese encephalitis virus and varicella zoster virus.[6,22,23,45-48]

Congenital infections. Congenital infection was the underlying cause of stroke in 3 children. The first 2 were a girl and a boy who presented with seizures at the ages of 5 months and 3 days. Subsequent radiological and serological investigations were compatible with an underlying congenital toxoplasmosis as being causative. The most characteristic change seen in this parasitic infection is the extensive necrosis of brain parenchyma due to vascular involvement by lesions. These are most intense in the basal ganglia, the cortex and at times in the periventricular areas.[49] Widespread cavitated necrosis may result from these destructive lesions and, when extensive, may amount to multicystic encephalomalacia or hydranencephaly.[50] Another 9-year-old boy who had left-sided hemiparesis, epilepsy and cognitive deficits had been serologically and radiologically diagnosed, at the age of 3 months, to have congenital rubella syndrome. Cranial CT scan revealed right cortical calcified schizencephalic defect with small thick gyri (associated with multiple calcifications). Cranial MRI at 9 years of age showed right cerebral, brain stem and cerebellar hemiatrophy and confirmed the presence of smooth thick gyri. Paucity of cerebral vessels on the right side was revealed by MRA. The above-mentioned radiological features are compatible with the presence of polymicrogyria, which are known to look macroscopically as abnormally broad gyri (pachygyria). Polymicrogyria frequently involve localized areas, which may correspond to arterial territories, especially of the MCAs.[51] Microgyria is known to result from perfusion failure following fetal infections,[52] which can produce vascular damage or circulatory insufficiency, and appears to be more important than cell destruction or secondary inflammatory damage in the genesis of congenital defects.[53] It is noteworthy that both congenital toxoplasmosis and rubella syndrome are potentially preventable through immunization, or other maternity health programs.[54]

Septicemia. Two patients developed stroke following febrile illnesses diagnosed to be septicemia, complicated by DIC in one of them. Cerebral infarct following septic shock is well recognized.[55] Also, DIC is a known risk factor for cerebral venous thrombosis.[26]

Neurobrucellosis. Stroke as a manifestation of neurobrucellosis deserves special consideration. Each of the 2 affected children had positive serology for brucellosis and showed clinical response to therapy. Examination of the CSF in the first patient revealed normal proteins, minimal pleocytosis, and Gram-negative coccobacilli. The second patient had normal CSF findings. Blood and CSF cultures yielded no growth in both patients who had been pre-treated for brucellosis. However, radiological investigations revealed lacunar and other infarcts involving mainly the deep cerebral nuclei, secondary to occlusion of small penetrating end arteries.[24] These lesions are reminiscent of those occurring following infection with another intracellular organism (namely, tuberculous meningitis). It has been reported that most of the cerebral infarctions due to tuberculous meningitis occur in the basal ganglia region.[56] The majority of autopsies in these cases revealed inflammation of the intracranial arteries and veins, sometimes associated with thrombosis and infarction.[57] Neither of the 2 patients, in this study, had evidence of coagulopathy nor endocarditis, either clinically, or following ECG and echocardiographic examinations. Reported neurological presentations of brucellosis in childhood, range from acute to chronic forms. The former includes meningitis and meningoencephalitis, whereas the latter includes behavioral disturbance,

brain abscess, myelitis, cerebellar ataxia (with or without cranial nerve involvement), radiculopathy and peripheral neuropathy.[58-66] Stroke as a complication of neurobrucellosis has been described in adults.[67-70] Occlusive vascular phenomena can result in episodes of monoparesis, hemiparesis and aphasia.[68,69] A case of cerebral hematoma due to rupture of a mycotic aneurysm after brucellar endocarditis has been described.[67] In a series on neurobrucellosis,[70] intracerebral and subarachnoid hemorrhage, from a presumed mycotic aneurysm, occurred in 2 of 4 patients with stroke. To the best of our knowledge, cerebrovascular disease as a manifestation of neurobrucellosis has not been reported in children, and is not mentioned in textbooks in pediatric cerebrovascular disorders.[24,71,72] Neurological complications in children with brucellosis are considered to be rare and account for <1% of pediatric brucellosis.[66] Clinically, neurobrucellosis can simulate several other neurological disorders, including tuberculous meningitis.[69] Correct diagnosis may be delayed. Caglar and Aysun[61] described 3 children with leptomeningitis due to brucellosis where the diagnosis was delayed for 1-2 months, and was correctly made in 2 cases only after bone marrow aspiration culture. Hence, it might be pertinent to recommend screening for brucellosis in childhood stroke, especially in Saudi Arabia where the infection is endemic. The dramatic favorable outcome following appropriate therapy, as seen in the second case, speaks for the importance of early diagnosis of the disease.

Inflammatory diseases. Systemic lupus erythematosus. In the 2 children with SLE, cerebrovascular disease manifested after 1-2 years from the initial diagnosis. Various neurological complications are known to result from SLE including arterial thrombosis, intracerebral hemorrhage, and sinovenous occlusion.[24,73-80] Symptoms of SLE can also be caused by infection, lupus cerebritis, complications of treatment or cerebral infarction secondary to the presence of antiphospholipid antibodies, Libman-Sacks endocarditis or thrombotic thrombocytopenic purpura.[73,74,81] It is noteworthy that the first of the 2 patients with SLE in this series had radiological features of ischemic changes following vasculitis; whereas the second one had bilateral subdural hygromas. However, ACA were present in the first patient and not detected in the second. Lupus anticoagulant was reported to occur in 39% of patients with SLE, and 43% were found to have ACA.[75,82] The chances of thrombosis could synergistically be enhanced by arteritis in a patient who had SLE and antiphospholipid antibodies.

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