Cardiac diseases as a risk factor for stroke in Saudi children

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ABSTRACT

Objective: To ascertain the role of cardiac diseases as a risk factor for stroke in a cohort of Saudi children who were evaluated in a retrospective and prospective study.

Methods: Children with cardiac diseases were identified from within a cohort of 104 Saudi children who presented with stroke. They were seen as inpatients in the Pediatric Wards or evaluated at the Outpatient Clinics of the Division of Pediatric Neurology (DPN), and the Division of Pediatric Cardiology at King Khalid University Hospital, Riyadh, Kingdom of Saudi Arabia during the periods July 1992 to February 2001 (retrospective study) and February 2001 to March 2003 (prospective study). A comprehensive form for clinical, neuroimaging, neurophysiological and laboratory data retrieval was designed and completed for each patient. Cardiac evaluation included 12-lead ECG and serial echocardiograms. Cardiac catheterization and 24-hour ambulatory ECG (Holter) were conducted on clinical discretion.

Results: Cardiac diseases were the underlying risk factor for stroke in 6 (5.8%) of the 104 children (aged one month to 12 years). The patients (4 males and 2 females) were evaluated at the DPN at a mean age of 5.3 years (range = 1 – 8 years; median 6.5 years). Onset of stroke was at a mean age of 34 months (range = 4 months - 8 years; median = 30 months). Five patients had stroke in association with congenital heart disease (CHD), whereas the sixth had restrictive cardiomyopathy. The identified CHD consisted of membranous ventricular septal defect in a 5-year-old boy who had moyamoya syndrome and sickle cell β^0-thalassemia, asymptomatic patent ductus arteriosus (PDA) in a 17-month-old girl, atrioventricular canal defect and PDA in an 8-year-old boy who also had Down syndrome, partial anomalous pulmonary venous drainage in a one-year-old boy, and Tetralogy of Fallot in an 8-year-old boy. The latter patient developed hemiparesis secondary to a septic embolus, which evolved into brain abscess involving the right fronto-parietal region. This was successfully managed surgically. The sixth patient was an 8 $^1/_2$-year-old girl who had hemiparesis and complex partial seizure in association with restrictive cardiomyopathy. Serial echocardiograms depicted resolution of the cardiac abnormalities within 5 years and subsequent normal findings.

Conclusions: Cardiac diseases, as a group, constitute a significant risk factor for stroke in Saudi children. Early diagnosis of these diseases is important to prevent further recurrences of stroke, and because some of them are potentially curable.

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Cardiac diseases, whether congenital or acquired, constitute a significant risk factor for stroke.[1-4] In large series,[4-8] cardioembolic and cyanotic congenital cardiac diseases accounted for nearly a fifth to a third of ischemic childhood strokes. Hypoxemia, manifested by microcytosis and relative anemia in children <4 years, and polycythemia in older children have also been identified as important associated

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risk factors.[9,10] The occurrence of congenital heart disease (CHD) was estimated to be 5-10 per 1000 live births.[11] When industrialized countries are excluded, rheumatic heart disease (RHD) continues to be a common cause of acquired cardiac morbidity and mortality in childhood, worldwide. It has been estimated that embolism in RHD is cerebral in 60%, peripheral in 30%, and visceral in 10% of cases.[12,13] Rheumatic valvular disease is a significant health problem in Saudi Arabia,[14] and is expected to have a significant contribution to the etiology of stroke. The mitral valve is the most commonly affected valve, followed by aortic and pulmonary valves. The presence of atrial fibrillation increases the risk for thromboembolism.[15] A cardioembolic stroke is known to complicate a right-to-left shunt, valvular disease, patent ductus arteriosus (PDA), thrombus or tumor in the left heart, endocardial disease, pulmonary arteriovenous fistula and cardiac surgery using cardiopulmonary bypass.[16,17] Many of the congenital and acquired structural cardiac lesions also cause chronic hypoxia and polythythemia. This makes it difficult to clinically distinguish thrombotic from embolic brain infarction.[18,19] Early correction of some congenital cardiac lesions may reduce the risk of stroke.[20,21] Paradoxical cerebral embolism occurs when emboli pass from the systemic venous circulation to the arterial circulation without being trapped in the pulmonary vascular bed.[22] This often results from congenital heart defects such as large septal defects, single ventricle, total anomalous pulmonary venous return or truncus arteriosus. Shunts across the ventricles include ventricular septal defect (VSD) and Tetralogy of Fallot (TOF); and shunts across the atria include atrial septal defect (ASD) and patent foramen ovale (PFO).[23-25] Infective endocarditis is an important cause of thromboembolism in patients who have congenital or acquired cardiac valvular disease.[26] Stenotic valves give rise to either bacterial or non-bacterial (marantic) vegetations.[27] Cardiomyopathies, whether dilated, restrictive, hypertrophic or obliterative increase the risk of embolism, because a poorly functioning, enlarged heart promotes intracardiac thrombi.[28] Cerebral embolism has been reported in a one-year-old child who had endocardial fibroelastosis.[29] After the first year of age, one of the most common cardiac operations for children with CHD is the Fontan operation. It consists of an anastomosis of the right atrium to the pulmonary artery. Stroke following the Fontan procedure is well-recognized.[30,31] It has been reported in 17 (2.6%) of 645 patients; the risk period of stroke extending from the first post-operative day to 32 months following surgery.[32] Another 6 (9.4%) of the 64 patients who survived the Fontan procedure had subsequent stroke with normal coagulation and hematologic parameters at the onset of the neurologic symptoms.[33] In the present study, we explore the role of cardiac diseases as a risk factor for stroke in a cohort of 104 Saudi children who were evaluated in a retrospective and prospective study on childhood stroke.

Methods. Children with cardiac diseases were identified from within a cohort of 104 Saudi children who presented with stroke during a prospective study extending for 2 years (February 2001 – March 2003) and a retrospective study, which spanned 8 years and 7 months (July 1992 – February 2001). They were seen as inpatients in the Pediatric Wards or evaluated at the Outpatient Clinics of the Division of Pediatric Neurology (DPN) and the Division of Pediatric Cardiology at King Khalid University Hospital (KKUH), Riyadh, Kingdom of Saudi Arabia. A comprehensive form for clinical, neuroimaging, neurophysiological and laboratory data retrieval was designed and completed for each patient. Details of these are depicted elsewhere.[34,35] The cardiac evaluation included medical history, physical examination, chest x-ray, standard 12-lead ECG and serial echocardiograms. Two-dimensional echocardiography and echo-Doppler studies were performed using Philips echocardiography machine (Model 5500). Multiple echocardiographic views were examined using colour flow to identify residual shunts. Blood flow velocities were assessed using Doppler-echocardiography. Cardiac catheterization and 24-hour ambulatory ECG (Holter) were conducted on clinical discretion.

Results. From a total of 104 children (aged one month to 12 years) with stroke, 6 (5.8%, 4 males and 2 females) had an underlying cardiac disease. Onset of stroke was at a mean age of 34 months (range = 4 months - 8 years, median = 30 months). They were evaluated at the DPN at a mean age of 5.3 years (range = 1-8 years, median = 6.5 years). The clinical characteristics of these patients are summarized in **Table 1**. Five patients had stroke in association with CHD, whereas the sixth had restrictive cardiomyopathy. The first patient (Patient 1, **Table 1**) was a boy who had his first stroke at the age of 3 years and later sustained multiple strokes, had epilepsy and was found to be mentally retarded. Brain MRI and magnetic resonance angiography (MRA), showed multiple infarcts, occlusion of both internal carotid arteries (ICA) at the level of the suprasellar region and early moyamoya changes. Details of these are depicted elsewhere.[35] His ECG showed features

Table 1 - Clinical characteristics of patients with an underlying cardiac risk factor for stroke.

Patient	Gender	Age at onset (years)	Age when evaluated at DPN (years)	Type of stroke	Underlying cardiac and other risk factors	Recurrence of stroke	Duration of follow-up (years)	Outcome
1	M	3	9	Arterial ischemic: Bilateral ICA, MCA, ACA occlusions. Early moyamoya changes	Membranous VSD. Sickle cell – β^0 thalassemia	Yes (moyamoya syndrome)	7.5	Alive
2	F	0.5	1.4	Left hemisphere infarct (MCA territory)	Asymptomatic PDA	No	6.7	Alive
3	M	3	8	Left frontoparietal infarct, basal ganglia calcification, bifrontal subdural hematoma	Atrioventricular canal defect, PDA, mild-pulmonary hypertension (corrected at 1 year of age)	No	5	Alive
4	M	0.3	1	Arterial ischemic: Encephalomalacia in left frontoparietal region	Partial anomalous pulmonary venous drainage	No	0.7	Alive
5	M	8	8	Septic embolism causing cerebritis/ brain abscess in right frontoparietal region	Tetralogy of Fallot	No	3	Alive
6	F	2	8.5	Lacunar infarcts in left and right parietal regions	Restrictive cardiomyopathy, dilated left atrium, mild mitral and tricuspid valves regurgitation	No	5	Alive

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

of biventricular hypertrophy associated with non-specific T wave changes. Echocardiography revealed a small peri-membranous VSD. This patient had another important hematologic risk factor, namely, sickle cell β^0-thalassemia.

The second patient was evaluated at the age of 17 months because of complex partial seizure and right hemiparesis, noticed from the age of 6 months. Cardiac assessment revealed an asymptomatic PDA. Electrocardiography depicted features of left ventricular hypertrophy. Echocardiography showed small PDA with left-to-right shunting (**Figure 1a**). Cranial CT showed an area of infarct involving the temporoparietal region. Brain MRI (**Figures 1b & 1c**) documented an old left hemisphere infarct, which was in the territory of the left middle cerebral artery (MCA), associated with dilatation of the left lateral ventricle. An MRA (**Figure 1d**) showed attenuated caliber of the left MCA with paucity of its branches.

Patient 3 (**Table 1**) was an 8-year-old boy, known to have Down syndrome, who had his first stroke at 3 years of age. He has been found to have mild pulmonary hypertension associated with atrioventricular canal defect and PDA. These were surgically corrected at the age of one year. Cranial CT, at 7 years of age, showed left frontoparietal old infarct, basal ganglia calcification (especially in the left lentiform nucleus) and bifrontal subdural hematoma. Echocardiography, when aged 11 years, showed moderate residual regurgitation of both repaired mitral and tricuspid valves (**Figure 2**).

The fourth patient (Patient 4, **Table 1**) was evaluated at 12 months of age for right hemiparesis associated with upper motor neurone right facial weakness. This had been noticed by his parents since the age of 4 months. Both cranial CT and MRI scans revealed an area of old encephalomalacia in the left frontoparietal region. Echocardiography showed features of

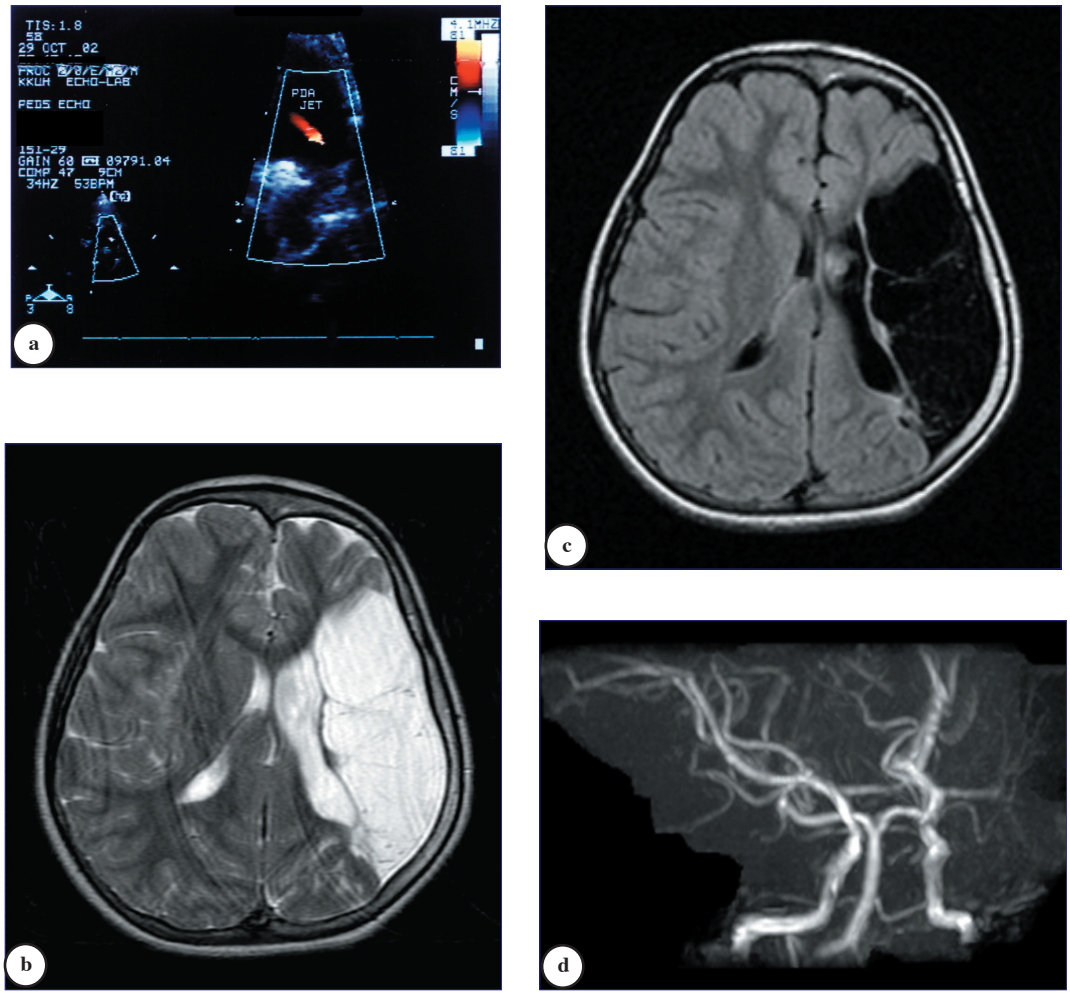

Figure 1 - **a)** Ductal view of 2D-echocardiography showing small PDA with left-to-right shunting. **b)** Axial T2-weighted brain MR image, and **c)** axial FLAIR image showing small left cerebral hemisphere, large left temporo-parietal cortical and subcortical cystic encephalomalacia due to old infarction along the left middle cerebral artery territory. **d)** MR angiography showing attenuated caliber of the left middle cerebral artery with paucity of its branches.

partial anomalous pulmonary venous drainage. One pulmonary vein (right lower) drained into the right atrium, whereas all other pulmonary veins drained into the left atrium. Interatrial and interventricular septa were apparently intact. No transesophageal echocardiography was carried out in this patient to ascertain the patency of foramen ovale.

An 8-year-old boy (Patient 5, **Table 1**) presented with left hemiparesis, which has been progressing over one week, associated with aphasia and neck stiffness. He was known to have TOF associated with cleft lip and palate. Corrective surgeries had been carried out for the facial defects and palliative cardiac surgery for his TOF in the form of Blalock-Taussig (BT) shunt. On examination, he was observed to be dysmorphic with dolichocephaly, low-set ears, downward slanting eyes, and evidence of repaired cleft lip and palate. Examination of the cardiovascular system showed the apex beat to be in the 5th intercostal space, and a systolic thrill was detected. The first heart sound was muffled, and the second was single. There was grade 4/6 continuous murmur (BT shunt murmur) and an ejection systolic murmur at the left upper sternal border. The liver was 2 cm below the costal margin. He had mild neck stiffness, left-sided hemiparesis with brisk deep tendon jerks. Investigations showed raised platelet count of 519 x 10^9/L (NR = 150-400) but otherwise normal complete blood count (CBC),

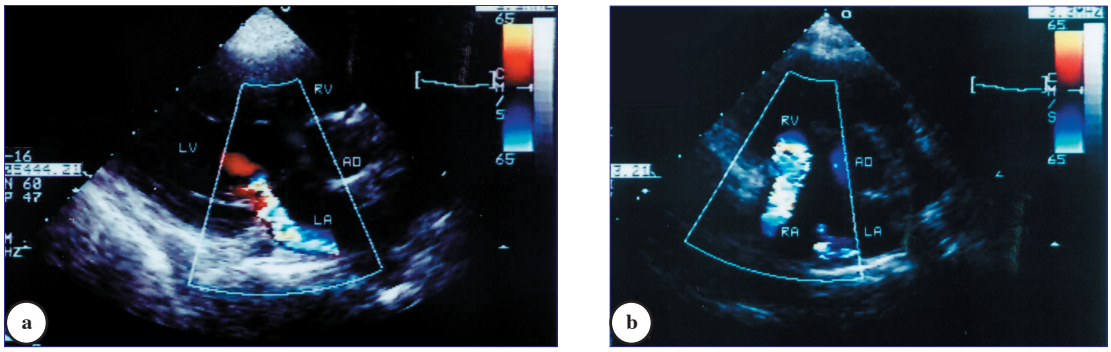

Figure 2 - Echocardiogram of Patient 3 (**Table 1**). **a)** Long axis view of the heart showing moderate mitral valve regurgitation. **b)** Short axis view of the heart showing moderate tricuspid valve regurgitation.

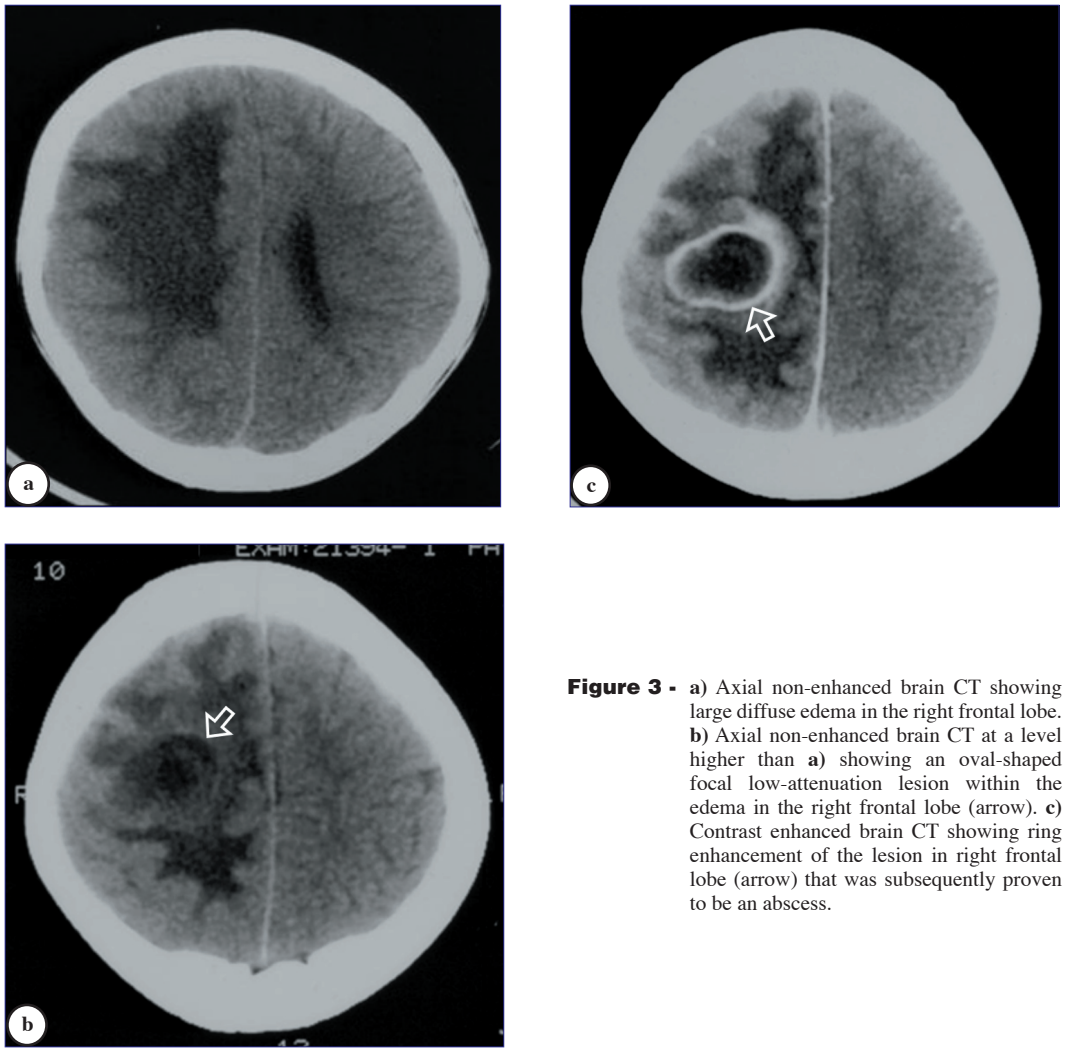

Figure 3 - **a)** Axial non-enhanced brain CT showing large diffuse edema in the right frontal lobe. **b)** Axial non-enhanced brain CT at a level higher than **a)** showing an oval-shaped focal low-attenuation lesion within the edema in the right frontal lobe (arrow). **c)** Contrast enhanced brain CT showing ring enhancement of the lesion in right frontal lobe (arrow) that was subsequently proven to be an abscess.

erythrocyte sedimentation rate (ESR) of 20 mm/hr (NR = 0-10); and normal prothrombin time (PT), and partial thromboplastin time (APTT). Other investigations, which were negative or revealed normal results, included anion gap estimation, random blood glucose, blood culture and hemoglobin electrophoresis. Electrocardiography showed sinus bradycardia (heart rate=59/min) and signs of right ventricular hypertrophy. Echocardiography revealed features of repaired TOF. Cranial CT (**Figures 3a & 3b**) depicted radiological signs of cerebritis/brain abscess involving the right frontoparietal region with midline shift and surrounding edema. Contrast-enhanced CT (**Figure 3c**) showed enhancement of the periphery of the lesion, with low-attenuation cavity. This was managed surgically, and cultures from the abscess revealed no bacterial growth. Cranial MRI, carried out 6 years later, showed an area of gliosis located in the right frontal lobe occupying the region of the precentral gyrus. Brain MRA was normal.

The sixth patient (Patient 6, **Table 1**) was seen at the DPN, when aged $8^1/_2$ years, because of complex partial seizure, starting at 7 months of age, and right-sided hemiparesis first noticed by her family at the age of 2 years. Cranial CT showed small infarct in the left parietal region. Brain MRI confirmed the CT findings and detected another lacunar infarct in the right parietal region. Electrocardiography showed evidence of left atrial enlargement. Echocardiography was reported to show restriction of left ventricle inflow and left ventricle diastolic dysfunction (restrictive pattern). A repeated echocardiogram, carried out after one year, showed dilated left atrium, mild mitral and tricuspid valves regurgitation, ejection fraction of 58%, shorting fraction 28% and improved function. Four years later, echocardiographic 4-chamber view of the heart showed normal chamber dimensions and no evidence of restrictive cardiomyopathy. It is noteworthy that the patient's family gave history of a 17-year-old brother who had surgery for the treatment of CHD. He remained well thereafter, and no medical reports were available to us for this sibling.

Discussion. The 6 children who had stroke with an underlying CHD illustrate the importance of this condition in the development of paradoxical cerebral embolism.[22] Paradoxical emboli are known to be associated with shunts across the ventricles; which include VSD (as in Patient 1, **Table 1**) and TOF (as in Patient 5). Patient 1 had another associated risk factor, (namely, sickle cell β^0–thalassemia); whereas Patient 5 had paradoxical septic embolus resulting in cerebral abscess. On the other hand, shunts across the atria include ASD and PFO. Reversal of the normal left-to-right shunting of blood occurs during a Valsalva maneuver, obstruction of ventricular outflow (for example, caused by pulmonary stenosis in TOF) and in some patients with pulmonary hypertension. It is noteworthy that Patient 2 had asymptomatic PDA. Patient 4 who had partial anomalous pulmonary venous return might have had PFO to account for the paradoxical stroke.[36] However, transesophageal echocardiography (the conclusive method for ascertainment of PFO)[37] was not carried out for this patient. Conversely, the PFO might have closed before the time of his evaluation.

As a poorly functioning heart promotes intracardiac thrombi, restrictive, dilated, hypertrophic or obliterative cardiomyopathies are associated with increased risk of cerebral embolism. This phenomenon manifested in Patient 6 (**Table 1**) who was found to have restrictive-pattern features of cardiomyopathy. Within 5 years, this was found to have resolved on follow-up echocardiography. For many years, it has been observed that dilated cardiomyopathy (DCM) is a frequent cause of heart disease in Saudi Arabia.[38] A resent study from the Eastern Province,[39] which evaluated 55 consecutive cases of DCM in patients <10 years of age, revealed important observations. The age of presentation was <30 months in 95% and 15 (27%) patients recovered from their illness. Complex segregation analysis of the family data showed evidence of autosomal recessive inheritance; an expected finding given the high rate of consanguinity in Saudi Arabia.[40] However, one of the known environmental factors for DCM, namely, selenium deficiency, was found in another study not to be a likely cause for the high incidence rate of DCM found in Saudi Arabia.[41]

The limited number of patients in this series who had stroke following CHD and the absence of RHD as a risk factor might not accurately reflect their prevalence in Saudi children.[42] This is because other specialized established centers within the Kingdom deal with the medical and surgical management of childhood cardiac disorders. Of 1052 patients (aged 1-90 years) who underwent 1522 valve procedures in one of these institutions,[43] the etiology was rheumatic in 68.8% and congenital in 11.4%. The total incidence of embolic events was 2.93%. In another study from the Eastern Province on 740 children with CHD,[44] who were studied over 3 years, VSD was the most common anomaly (39.5%), and was followed in descending order of frequency by ASD, pulmonary stenosis and PDA. Down syndrome was the most common associated underlying disorder, as has been the case with Patient 3 (**Table 1**). Data

collected on 891 consecutive patients with CHD in another large tertiary center in Riyadh,[45] suggested that first-cousin marriage may be a significant risk factor for specific types of CHD in Saudi Arabia. The proportion of first cousins in the CHD group was higher than the proportion in the general population suggesting the involvement of an autosomal recessive gene in the pathogenesis of CHD. Also, first-cousin consanguinity was significantly associated with VSD, ASD, pulmonary stenosis, and pulmonary atresia.

In conclusion, cardiac diseases constitute, as a group, a significant risk factor for stroke in Saudi children. Early diagnosis and management of these will contribute to the primary prevention of stroke and prevent further recurrences.

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