

# Congenital and genetic cerebrovascular anomalies as risk factors for stroke in Saudi children

*Mustafa A. Salih, Dr Med Sci, FRCPCH, Waleed R. Murshid, FRCSEd, FRCS (SN), Jihad N. Zahraa, MD, Abdel-Galil M. Abdel-Gader, PhD, FRCP, Ahmed A. Al-Jarallah, MBBS, ABP, Amal Y. Kentab, KSFP, MRCP (UK), Ibrahim A. Alorainy, MD, Hamdy H. Hassan, FRCR, Giap T. Tjan, MD.*

## ABSTRACT

**Objective:** To explore the role of and report on congenital and genetic cerebrovascular anomalies as risk factors for stroke in a prospective and retrospective cohort of Saudi children.

**Methods:** Children with stroke were evaluated at the Division of Pediatric Neurology (DPN), or were seen as inpatients in the Pediatric Wards at King Khalid University Hospital (KKUH), Riyadh, Kingdom of Saudi Arabia during the periods July 1992 to February 2001 (retrospective study) and February 2001 to March 2003 (prospective study). Stroke work-up for each suspected case included hemostatic assays, serological, biochemical and neurophysiological tests. Neuroimaging modalities included routine skull x-rays, CT, MRI, magnetic resonance angiography (MRA) and conventional cerebral angiography.

**Results:** Of 104 children with stroke, congenital and genetic cerebrovascular anomalies were the underlying risk factor in 7 (6.7%). The patients were evaluated at the DPN at a mean age of 66 months (range = 8 months to 11 years, median = 6 years); and they had stroke at a mean age of 48 months (range = 2 months to 10 years, median = 8 months). Four patients had stroke in association with neurocutaneous syndromes. Two had Sturge-Weber syndrome (SWS), one

had Klippel-Trenaunay syndrome associated with SWS, and the fourth had neurofibromatosis type 1. Two patients had intracranial hemorrhage secondary to ruptured aneurysm. A girl (aged 9 years and 4 months) had left posterior cerebral artery aneurysm. She was diagnosed to have autosomal dominant polycystic kidney disease following renal ultrasonography. She died 5 months later despite surgical intervention (clipping of aneurysm). The second child was an 8-month-old boy who presented with subarachnoid and intraventricular hemorrhage (IVH) following ruptured anterior communicating artery aneurysm. He recovered with no residual symptoms following successful clipping of the aneurysm. Arteriovenous malformation (AVM) caused IVH in a 7-year-old boy who reported to hospital 5 hours after onset of headache, vomiting, drowsiness, and dizziness. Following drainage of the IVH and stabilization of the patient, the AVM was successfully embolized 6 weeks later.

**Conclusions:** As a group, congenital and genetic cerebrovascular anomalies constitute a significant risk factor for stroke in Saudi children. Recognition of these diseases is important since some are treatable and because other family members may be at risk.

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A variety of congenital cerebrovascular anomalies are known risk factors for stroke in children.<sup>1</sup>

These include Sturge-Weber syndrome (SWS),<sup>2,3</sup> intracranial aneurysm,<sup>4</sup> arteriovenous malformation

From the Division of Pediatric Neurology (Salih, Al-Jarallah, Kentab), Department of Pediatrics, Division of Neurosurgery (Murshid), Pediatric Intensive Care Unit (Zahraa), Department of Physiology (Abdel-Gader), Department of Radiology (Alorainy, Hassan), College of Medicine, King Saud University, Department of Neuroradiology (Tjan), Armed Forces Hospital, Riyadh, Kingdom of Saudi Arabia.

Address correspondence and reprint request to: Prof. Mustafa A. M. Salih, Division of Pediatric Neurology, Department of Pediatrics, College of Medicine, PO Box 2925, Riyadh 11461, Kingdom of Saudi Arabia. Fax: +966 (1) 4679463. E-mail: mustafa@ksu.edu.sa

(AVM),<sup>5</sup> cavernous angioma<sup>6</sup> and hereditary hemorrhagic telangiectasia (Rendu-Osler-Weber syndrome).<sup>7,8</sup> In addition to SWS, other neurocutaneous syndromes associated with childhood stroke include neurofibromatosis,<sup>9-12</sup> Ehlers-Danlos type IV,<sup>13</sup> Fabry disease,<sup>14,15</sup> and pseudoxanthoma elasticum.<sup>16</sup> As a group, they constitute a significant genetic risk factor for cerebrovascular disease.<sup>1,17</sup> Most of them are caused by a mendelian disorder (usually inherited as autosomal dominant).<sup>1,8</sup> Recognition of these diseases is important since some are treatable and because other family members may be at risk.<sup>18,19</sup> In this report, we explore the role of congenital and genetic cerebrovascular anomalies as risk factors in a cohort of 104 Saudi children who were seen during a prospective and retrospective study on childhood stroke.

**Methods.** Children with congenital and genetic cerebrovascular anomalies were identified from within a cohort of 104 Saudi children 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 evaluated at the Outpatient Clinics of the Division of Pediatric Neurology (DPN), or were seen as inpatients in the Pediatric Wards at King Khalid University Hospital (KKUH), Riyadh, Kingdom of Saudi Arabia. The salient demographic, clinical, neuroimaging, neurophysiological and laboratory data were retrieved in a specially designed comprehensive protocol. Details of these, as well as the laboratory methods and statistical analyses are depicted elsewhere.<sup>20,21</sup>

**Results.** From a cohort of 104 Saudi children (aged one month to 12 years), 7 (6.7%, 4 males and 3 females) had stroke secondary to congenital or genetic cerebrovascular anomalies, or both, at a mean age of 48 months (range = 2 months to 10 years; median = 8 months). They were evaluated at the DPN at a mean age of 66 months (range = 8 months – 11 years; median = 6 years). The clinical characteristics of these patients are summarized in **Table 1**. Four patients had stroke in association with neurocutaneous syndromes. Two had Sturge-Weber syndrome (SWS), one had Klippel-Trenaunay syndrome (KTS, OMIM 149000) associated with SWS, and the fourth had neurofibromatosis type 1. Patient one (**Table 1**) with SWS had hemorrhagic infarct involving the left frontal and left parietal lobes. He had flat facial angiomatous nevus on the upper left side of the face, which was getting smaller with time. He also had complex partial seizures. Electroencephalography (at the age

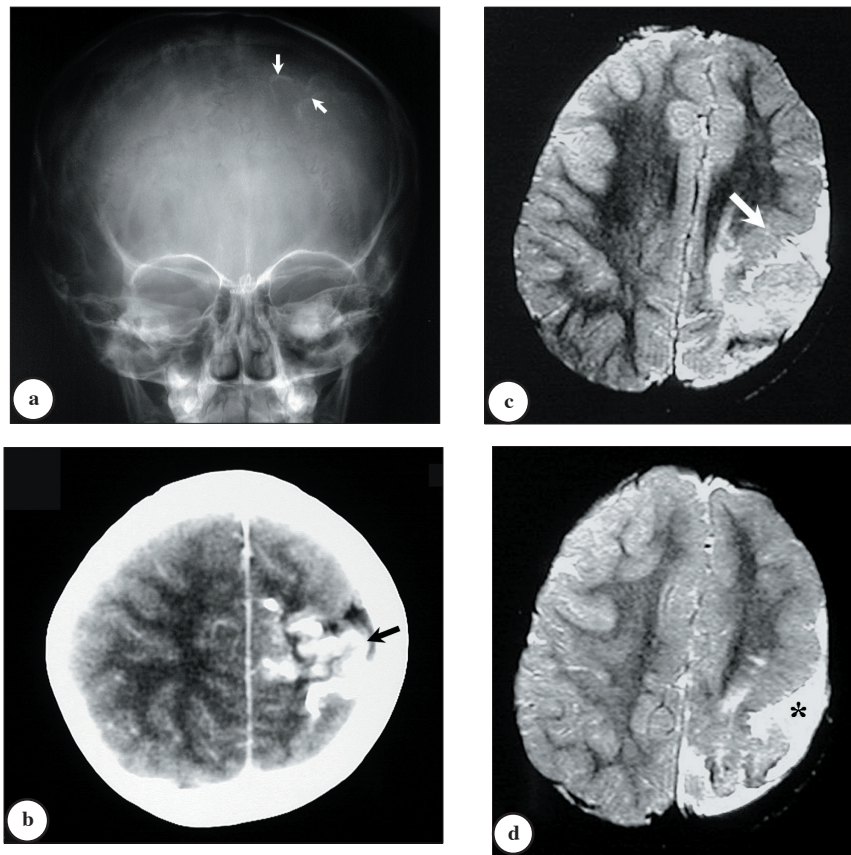
of 28 months) showed asymmetric background with slowing in the left side. There were frequent bursts of generalized discharges of spikes and multifocal slow waves, lasting for <1 second and starting from the left. Cranial CT showed left frontal gyral calcification; whereas MRI revealed left fronto-temporo-parietal pachygyria associated with large cisterna magna. The second patient with SWS (Patient 2, **Table 1**) had flat facial angiomatous nevus, which also involved the head (mainly on the left side). Skull x-ray (**Figure 1**) at 6 years of age showed the “railroad track pattern” calcification in the left temporo-parietal region. Cranial CT (at 6½ years of age) showed atrophy of the left cerebral hemisphere associated with gyral calcification of the left temporoparietal region (**Figure 1**). Brain MRI (**Figure 1**) showed left parietal, schizencephaly-like, brain defect with grey matter lining associated with occipitoparietal focal atrophy. Patient 3 (**Table 1**) had KTS with angiomatous skin lesions involving the face, the right hand, and right leg, associated with right side hemihypertrophy. He also had hydrocephalus, managed at the age of 10 months with a left-sided ventriculoperitoneal shunt, and right eye glaucoma manifesting as buphthalmos. The child was referred from the neurosurgery service at the age of 23 months because of severe refractory complex partial seizures (left focal with secondary generalization). Subsequently, this was successfully controlled following multiple anti-convulsant therapy. Electroencephalography showed asymmetric background with low voltage slow waves on the right side. There were also sporadic sharp waves seen on the left side. He had multiple cranial CT scans carried out at ages of 4, 13, and 16 months. Gyral calcification was seen in the latter examination (when aged 16 months). A brain MRI (at 16 months of age) showed features of bilateral chronic subdural hematoma encircling the brain and extending to the falx cerebri and tentorium cerebelli. There was brain atrophy associated with features of gliosis at the right peritrigonal region, right choroids plexus cyst, and calvarial thickening. Echocardiography and ECG were normal. Residual sequelae observed over the following 43 months consisted of left hemiparesis and dysphasia. An 11-year-old girl (Patient 4, **Table 1**) was seen at the DPN because of right hemiparesis, which presented one year back, with headache and right-sided focal seizures. She used to have recurrent right-sided focal convulsions since 6 months of age. Physical examination revealed uncountable café au lait spots of which more than 5 had a diameter of >5 mm. There were also 2 subcutaneous neurofibromas in the right thigh. Contrast-enhanced MRI of the brain showed left middle cranial fossa moderate sized arachnoid

**Table 1** - Clinical characteristics of patients with congenital and genetic cerebrovascular anomalies.

Patient	Gender	Age at onset of initial stroke (years)	Age when evaluated at DPN (years)	Type of stroke	Underlying/ associated conditions	Neurological symptoms and signs at presentation of initial stroke	Surgical management	Outcome
1	M	0.3	2.3	Hemorrhagic infarct: left frontal and left parietal lobes	Sturge-Weber syndrome	Irritability, generalized seizures, right-sided hemiparesis	None	Alive
2	F	0.2	6	Arterial ischemic: left temporoparietal region	Sturge-Weber syndrome	Right-sided seizures, right hemiparesis	None	Alive
3	M	0.3	1.9	Hemorrhagic: bilateral chronic subdural hematoma extending to falx cerebri and tentorium cerebelli	Klippel-Trenaunay syndrome + Sturge-Weber syndrome	Left hemiparesis, macrocephaly	Ventriculo-peritoneal shunt	Alive
4	F	10	11	Arterial ischemic: Left temporal lobe, left middle cerebellar peduncle and left hemisphere	Neuro-fibromatosis type 1	Headache, right-sided hemiparesis	None	Alive
5	F	9.3	9.3	Intracranial hemorrhage secondary to left PCA aneurysm bleed	Adult type polycystic kidney disease	Coma	Clipping of aneurysm	Died 5 months after initial hemorrhage
6	M	0.7	0.7	Subarachnoid and intraventricular hemorrhage following ruptured ACA aneurysm	None	Vomiting, irritability, right-sided seizures with secondary generalization, right hemiparesis	Clipping of aneurysm	Alive
7	M	7	7	Intraventricular hemorrhage following left parietal AVM	None	Headache, vomiting, drowsiness, dizziness	Embolization of AVM	Alive
DPN - Division of Pediatric Neurology, PCA - Posterior cerebral artery, ACA - Anterior communicating artery, AVM - Arteriovenous malformation								

cyst with mild to moderate left temporal lobe atrophic changes. There was also white matter hyperintensity seen on T2-weighted and fluid-attenuated inversion recovery (FLAIR) images in the left temporal lobe, left middle cerebellar peduncle and left hemisphere. In addition, several hamartomatous brain lesions were also seen in the region of the left basal ganglia. Two patients had intracranial hemorrhage secondary to ruptured cranial aneurysm. The first (Patient 5, **Table 1**) presented at the age of 9 years and 4 months with intracranial hemorrhage secondary to left posterior cerebral artery (PCA) aneurysm. Conventional 4-vessel cerebral angiography showed an oblong bilobed aneurysm in the junction of the left posterior cerebral and posterior choroidal arteries. There was no

associated spasm or mass effect. She was diagnosed to have autosomal dominant polycystic kidney disease (ADPKD) following renal ultrasonography. She died 5 months later despite surgical intervention (clipping of aneurysm). The second child (Patient 6, **Table 1**) was an 8-month-old boy who presented with subarachnoid and intraventricular hemorrhage following rupture of anterior communicating artery (ACA) aneurysm. He underwent conventional 4-vessel cerebral angiography, which delineated the ACA aneurysmal dilatation. Ultrasound of the kidneys was negative for polycystic kidney disease and echocardiogram was normal. He recovered with no residual symptoms following successful clipping of the aneurysm. Details of the management of the



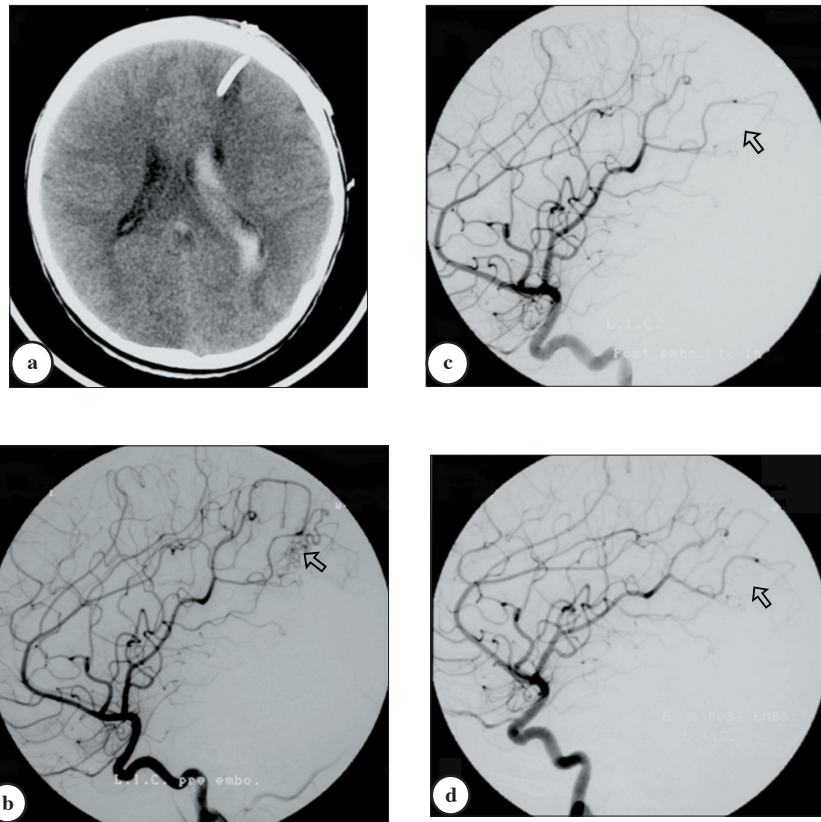
**Figure 1** - **a**) Occipitofrontal view of the skull showing “railroad track pattern” calcification in the left parietal region (arrows). **b**) Axial brain CT showing atrophy of the left cerebral hemisphere and gyral calcification in the left parietal region (black arrow). **c & d**) brain MRI (axial T2-weighted images) showing left temporoparietal schizencephaly (asterisk) with grey matter lining (arrow), associated with left posterior parietal and occipital atrophy.

child have been reported elsewhere.<sup>22</sup> Patient 7, **Table 1** was admitted 5 hours after onset of headache, vomiting, drowsiness and dizziness. Cranial CT scan revealed intraventricular (IVH) hemorrhage (**Figure 2**). Laboratory investigations showed normal complete blood count (CBC), prothrombin time (PT), partial thromboplastin time (APTT) and blood culture. Ventricular tap was bloody. A 4-vessel cerebral angiography revealed left parietal AVM. Following drainage of the IVH and stabilization of the patient, including blood transfusion, the AVM was successfully embolized 6 weeks later (**Figure 2**). He recovered without residual symptoms or signs.

**Discussion.** Of the cohort consisting of 104 Saudi children with stroke, congenital and genetic cerebrovascular anomalies were the underlying risk factors in 7, a significant proportion. Four of the affected 7 had an identified neurocutaneous syndrome.

Sturge-Weber syndrome (SWS, OMIM 185300) was the underlying cause of stroke in 2 children, and was associated with KTS (OMIM 149000) in a third. Sometimes called the fourth phacomatosis, SWS is characterized by nevus flammeus of the face and angioma of the meninges, usually ipsilateral to the facial lesion. Klippel-Trenaunay syndrome (KTS), on the other hand, clinically resembles SWS, and is characterized by large cutaneous hemangioma with hypertrophy of the related bones and soft tissue.<sup>23,24</sup> The 2 conditions are associated in some cases.<sup>25</sup> The nevus flammeus in SWS classically involves the forehead and upper eyelid, but often affects both sides of the face.<sup>26</sup> It is cranial in 99%, and 45% of cases also have extracranial nevi over the torso, extremities, or both.<sup>27</sup> When involving the forehead, it is associated with leptomeningeal angioma in 10-20% of children.<sup>28</sup> Although any part of the brain can be affected, the parietal and occipital lobes (as





**Figure 2 -** a) Axial non-enhanced brain CT showing hemorrhage in the left lateral ventricle and ventricular drainage tube. b) Digital subtraction angiogram showing arteriovenous malformation (AVM) in the left parietal region (arrow). c) Disappearance of the AVM immediately post-embolization, and d) 6 months later (arrow).

in Patient 2, **Table 1**) are more often involved by the leptomeningeal angioma than the frontal lobes (as seen in Patient 1, **Table 1**). Cerebral atrophy, especially adjacent to the angioma, is typical and presented in Patient 2 (**Table 1**) as schizencephaly-like brain defect. Gyral calcification, which was shown in the 2 children as well as in Patient 3 (**Table 1**) with associated KTS, results from deposition of calcium within the outer cortical layers.<sup>29,30</sup> Calcification may become more apparent with age, as has been the case with Patient 3 (**Table 1**), where gyral calcification was seen on CT scans carried out at the age of 16 months, but not earlier at 13 or 4 months of age. However, calcification is sometimes present at birth and can be demonstrated much earlier with CT than with standard skull X-rays.<sup>31-33</sup> A skull x-ray carried out for Patient 2 (**Table 1**) at 6 years of age showed the characteristic “railroad track pattern” (**Figure 1**). The abnormal intracranial vessels can be effectively shown by MRI with gadolinium contrast enhancement whereas magnetic resonance angiography (MRA) may show

the larger abnormal vessels. It is noteworthy that one of the patients (Patient 3, **Table 1**) showed right choroidal plexus cyst corresponding to the affected hemisphere. Enlargement of choroids plexus in the hemisphere affected with SWS, has been reported in children.<sup>34</sup> Depending on the site of intracranial vascular lesions in SWS, focal neurological deficits occur. Hemiparesis often develops acutely in conjunction with the initial bout of seizures, as has been depicted in Patients one and 2 (**Table 1**). In Patient 3, (**Table 1**), the left hemiparesis preceded his initially refractory complex partial seizures, as has been observed in other cases by Roach and Reila.<sup>1</sup> Repeated venous occlusion may account for the motor deficit in the latter 2 patients.<sup>2</sup> Intracranial hemorrhage due to SWS is rare.<sup>1</sup> In a large series, seizures were present in 80% of children (87% of those with bilateral and 71% of those with unilateral nevus flammeus).<sup>27</sup> Reduced amplitude adjacent to the leptomeningeal angioma is often revealed by EEG, as has been shown in Patient 3 (**Table 1**). Focal epileptiform discharges may be observed

ipsilateral (as in Patient 1, **Table 1**) or contralateral to the affected sphere.<sup>35,36</sup> Occasionally, and with radiological involvement of one sphere, bilateral synchronous discharges are recorded.<sup>37</sup> With the help of EEG, prompt management of epilepsy is more likely to be achieved through guiding anticonvulsant medication.<sup>1</sup> Control of epilepsy is rewarding, since the earlier onset of seizures and longer duration have been shown to affect adversely the cognitive outcome of children with SWS.<sup>27</sup> Another important morbidity associated with SWS, is glaucoma (as seen in Patient 3, **Table 1**) which has been reported in 48% of children, being unilateral in 67% of those affected.<sup>27</sup> Early diagnosis can be achieved through periodic measurement of the intraocular pressure. In the large surveys by Sujansky and Conradi,<sup>27</sup> glaucoma was diagnosed during the first year of life in 61% and by 5 years in 72%.

Neurofibromatosis type 1 (NF1), complicated by right hemiparesis, was seen in an 11-year-old girl (Patient 4, **Table 1**). She had multiple lacunar infarcts in the left temporal lobe, left middle cerebellar peduncle and left hemisphere. Neurovascular abnormalities associated with neurofibromatosis include moyamoya syndrome, hypertensive stroke, aneurysm or arteriovenous fistula.<sup>12,38-40</sup> Stroke with resulting hemiparesis has been reported to occur as early as 7 weeks of age and prior to the development of other manifestations of NF1.<sup>11</sup> Lacunar infarcts have also been reported. In one of the large studies of NF1,<sup>10</sup> one patient (aged 19 years) had a left hemiparesis related to a lacunar stroke of unknown origin.

Three children in this study presented with intracranial hemorrhage secondary to aneurysm or AVM. In large series and population studies, vascular anomalies including arterial aneurysms, AVM, cavernous malformation and arteriovenous fistula constituted between 43-67% of childhood brain hemorrhage.<sup>41,42</sup> In the present study, a 9-year and 4-month-old girl had intracranial hemorrhage secondary to a ruptured aneurysm of the PCA, whereas another 8-month-old-boy presented with subarachnoid hemorrhage and IVH following ruptured ACA aneurysm. Symptomatic intracranial aneurysms are rare in childhood,<sup>4</sup> and <2% rupture before the age of 19 years. During the first 2 decades they present in a biphasic mode with the lesions often becoming symptomatic before the age of 2 or after the age of 10 years.<sup>43</sup> In both children and adults, subarachnoid hemorrhage is the most common initial manifestation of intracranial aneurysm; although intraparenchymal or intraventricular hemorrhage, often combined with subarachnoid hemorrhage, occurs in many patients.<sup>1,44</sup>

The first child with intracranial hemorrhage in the current study, presented with loss of consciousness (coma) whereas the second boy presented with irritability, vomiting, focal seizures and hemiparesis. Sudden onset headache, vomiting and deterioration of consciousness are typical presentations of subarachnoid hemorrhage.<sup>1</sup> Focal or generalized seizures occur in 11-25% of patients, and may be more common in infants than adults.<sup>44-46</sup> Prompt seizure control is vital in children with aneurysm to prevent additional bleeding secondary to raised arterial blood pressure during an epileptic fit.<sup>1</sup> Intracranial aneurysms have been found in patients with several other congenital disorders.<sup>1</sup> One of the most common associated disorders is polycystic renal disease, as has been the case in Patient 5 (**Table 1**). The ADPKD accounts for the majority of the cases associated with intracranial aneurysm, and usually presents after the second decade.<sup>47,48</sup> A large series<sup>49</sup> on pediatric ADPKD documented the phenotypic heterogeneity at the time of first presentation. A family history of ADPKD was known at presentation in 89%, whereas 5% had no known family history of the disease. It should be emphasized that pediatric patients with ADPKD should be screened, noninvasively, with three-dimensional (3D) CT angiography or MRA to detect intracranial aneurysm and prevent a serious and potentially fatal outcome.<sup>50</sup> However, aneurysms are rare with infantile type polycystic kidney disease, which is inherited as autosomal recessive, and usually presents with a flank mass or enlarging abdomen, and has short life expectancy.<sup>51</sup> The third child with hemorrhagic stroke and a vascular malformation presented at the age of 7 years with headache, vomiting and dizziness. A cranial CT scan showed intraventricular hemorrhage that was subsequently found, by conventional angiography, to be due to left parietal AVM. Children with AVM are more likely to present with hemorrhage than adults and AVM accounts for 30-50% of hemorrhagic stroke in children.<sup>52-55</sup> Such hemorrhagic events have been associated with a 25% mortality rate.<sup>56</sup> In a multi-centre study from Saudi Arabia,<sup>5</sup> childhood ( $\leq 16$  years) intracranial AVM accounted for 7.7% of all AVM cases. For the radiological diagnosis of intracranial aneurysms and AVM, initial cranial CT scan is mandatory. In case of aneurysms, it demonstrates subarachnoid hemorrhage, defines the extent and sometimes the source of bleeding, and depicts an associated edema, infarction or hydrocephalus.<sup>1</sup> However, CT is less reliable after 5 days from the onset of subarachnoid hemorrhage and milder hemorrhages might not be visible.<sup>1,57</sup> On the other hand, AVM frequently contains calcified areas which are visible on CT. Also CT scan can reveal

intraparenchymal or intraventricular hemorrhages, as depicted in 2 of our patients.<sup>1</sup> Giving intravenous contrast usually highlights the lesion. Smaller lesions may be missed by CT if non-calcified or intermingled with an acute intraparenchymal hemorrhage.<sup>1,58</sup> Magnetic resonance imaging identifies AVM as flow void areas created by the rapidly moving blood within the lesion, but can also miss small ones.<sup>1</sup> When intracranial hemorrhage is diagnosed, especially in the out-of-hours setting, MRA is an attractive alternative to conventional angiography. A comparative study<sup>59</sup> showed conventional angiography to be superior to MRA in demonstrating arterial anatomy except for the anterior and posterior communicating arteries where MRA was superior. Also, MRA had high sensitivity in detection of arteriovenous malformations similar to conventional angiography. Nevertheless, conventional angiography remains the most accurate means of confirming AVM and outlining its location and blood supply.<sup>60</sup> It is also vital in the investigation of suspected aneurysms since there is always the possibility of multiple intracranial aneurysms and the frequent variations from the usual cerebral vascular pattern.<sup>1,61,62</sup> However, a recent study<sup>63</sup> reported that multiple ACA aneurysms could be better identified using 3D CT angiography. The gloomy outlook for patients with aneurysm who do not have a devastating initial hemorrhage, has changed greatly following improvements in diagnostic methods, neurosurgical techniques and improved anesthetic management.<sup>64,65</sup> This has been reflected in the 8-month-old boy in this series who had successful surgical obliteration for ACA aneurysm. On the other hand, a multidisciplinary approach is needed for the treatment of AVM to guide the choice of one or a combination of therapeutic options.<sup>55,66</sup> These include the use of endovascular techniques, radiosurgery, open surgery, and observation.

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