

# Pial Arteriovenous Fistula and Capillary Malformation-Arteriovenous Malformation Associated with *RASA1* Mutation: 2 Pediatric Cases with Successful Surgical Management

A. Jessey Chugh Asim Shahid Sunil Manjila Deepak Gulati  
Nicholas C. Bambakidis

Division of Pediatric Epilepsy, Department of Pediatric Neurology, Rainbow Babies and Children's Hospital, and Department of Neurology and Neurosurgery, The Neurological Institute, University Hospitals Cleveland Medical Center, Cleveland, OH, USA

## Established Facts

- In the setting of characteristic multifocal capillary malformations with or without known arteriovenous malformations, *RASA1* mutations should be included in the differential.
- Clinical presentation can include altered mental status, seizures, macrocrania, and/or focal neurological deficits.

## Novel Insights

- Low threshold should be held for advanced vascular imaging – both intra- and extracranial – in patients with this condition.
- Surgical clipping, although invasive, can allow for more definitive control of the intracranial shunt as opposed to other techniques.

## Keywords

Pial arteriovenous fistula · Telangiectasia · Capillary malformation · Arteriovenous malformation · *RASA1* mutation

## Abstract

We present case reports of 2 pediatric patients who were both found to have pial arteriovenous fistulas (AVFs) with subsequent genetic analysis revealing mutations in the *RASA1* gene. Considering their family history of distinct cutaneous lesions, these mutations were likely inherited as op-

posed to de novo mutations. Patient 1 had large capillary malformations on the left side of the face and neck, associated with macrocephaly, and presented at the age of 32 months with speech delay, right-sided weakness, and focal seizures involving the right side of the body. Patient 2 presented with proptosis at the age of 9 months, but was otherwise neurologically intact. Given the chance for definitive single-stage control of vascular shunt (obviating chances for radiation exposure with endovascular treatment) and surgically accessible location of these intracranial lesions, both patients were treated with surgery with excellent clinical and radiological outcome. In general, given the high mortal-

ity secondary to severe congestive heart failure when treated conservatively, the goal of treatment in cortical AVF in young children, even when asymptomatic, is rapid control of the shunt. This was achieved successfully in our cases – both patients experienced significant symptomatic improvement following surgery and remained neurologically stable in the subsequent follow-up visits.

© 2017 S. Karger AG, Basel

## Introduction

Pial arteriovenous fistulas (pAVFs) and capillary malformation-arteriovenous malformations (CM-AVMs) are recently identified categories of intracranial vascular pathologies similar to AVMs, cavernomas, and telangiectasias. CM-AVM is a newly recognized entity caused by mutations in the *RASA1* gene. pAVFs have also been found to be associated with this gene [1]. The *RASA1* gene (Ch. 5q13.3.1) encodes the p120-RasGTPase-activating protein, whose primary function is negative inhibition of the Ras/MAPK-signaling pathway. This pathway is important for cell growth and differentiation. AVMs and AVFs are generally classified as fast-flow vascular lesions that can arise in any tissue and cause life-threatening processes including hemorrhage, CHF, or neurologic sequelae. In CM-AVM, these arteriovenous abnormalities are typically macrofistulas and usually present with neurologic signs at birth or before 1 year of age. However, the most prominent features in patients with this disease entity are small, usually multifocal, and randomly distributed cutaneous CMs [2]. In general, the prevalence of brain AVMs is reported to be around 10/100,000 [3].

Pediatric pAVFs (also known as nongalenic pAVFs) are also rarely reported to be associated with *RASA1* mutations [3]. These should be distinguished from dural AVFs since the fistula site is within the subpial meningeal space and there is a lack of direct involvement of the embryonic median prosencephalic vein. The prevalence of the intracranial pial fistulas is suspected to be 0.1/100,000 to 1/100,000. According to data referenced in one study, a total of 168 cases of intracranial pAVFs have been reported since 1970, making this entity quite rare [3]. The association with hereditary hemorrhagic telangiectasia, also known as Osler-Weber-Rendu syndrome, has been reported to be up to 25%. One particular study followed 7 patients with this disease entity and found that 2/7 harbored a mutation in the *RASA1* gene while 0/7 had hereditary hemorrhagic telangiectasia [1]. In terms of

clinical presentation, infants tend to present initially with CHF and may have macrocrania or focal neurological deficits. The goal of treatment is occlusion of the AVF site or of the feeding arteries and proximal drainage vein as close to the fistula as possible. Prognosis is considered to be poorer with conservative management, and treatment is usually pursued unless significant brain damage has already occurred [3]. We describe successful surgical treatment of 2 patients with CM-AVM and pAVF associated with *RASA1* mutation.

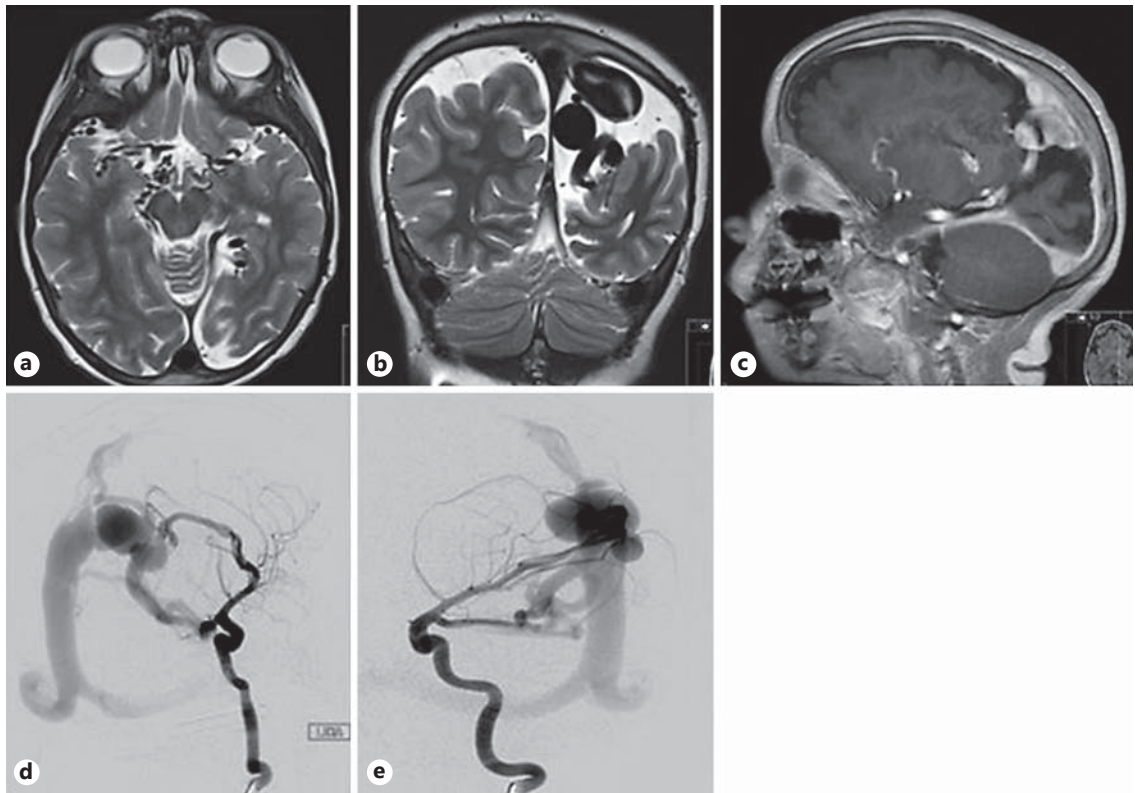
## Illustrative Cases

### Case 1

#### History and Examination

This African-American male patient was first seen at the age of 32 months by a pediatric neurologist for the evaluation of macrocephaly, multiple café-au-lait spots, and left facial neck angiomas. At that time, there was no concern for seizures or other abnormal movements. Five months later, the patient presented again to the same physician with multiple episodes of sudden falls and loss of strength in the right arm and leg with jerking. Further history revealed that the patient was born 5 days after term via normal vaginal delivery with no perinatal complications. Development had been age appropriate with the exception of delayed speech and right hemiparesis. Family history was not significant for epilepsy, but the mother reportedly had CM lesions on her skin. On examination, multiple café-au-lait spots were noted on the bridge of the left side of the nose as well as on the left mandible. More of these spots were present on the extremities – lower extremities more than the upper. The rest of the patient's physical examination was unremarkable. He ultimately underwent epilepsy monitoring, which confirmed focal left hemisphere epilepsy with subsequent initiation of levetiracetam. Due to the combination of skin lesions, epilepsy, speech delay, macrocephaly, and a family history of cutaneous CM, genetic testing was done via a microarray analysis revealing a mutation in the *RASA1* gene.

Initial MRI of the brain showed a malformed, hypoplastic left parietal lobe with additional, milder involvement of the left temporal and occipital lobes. Fairly extensive left hemispheric polymicrogyria and gliosis was noticed. An additional suspected focus of polymicrogyria and gliosis in the right parietal parasagittal region was also observed. Numerous prominent and serpiginous intracranial vessels, both arterial and venous, suggestive of continued congenital arteriovenous malformation were present. At a subsequent neurology outpatient consultation 3 months later, the patient was noted to have slight hemiparesis in the right upper extremity. He also had seizures characterized by staring, gazing, and drooling with weakness of the right side with no clear motor phenomenon. Repeat MRI at that time showed a left parietal arteriovenous fistula with a large left parietal varix, which appeared partially thrombosed. Cerebral angiography confirmed a pAVF in the left parietal region. There was also the presence of multiple enlarged feeders arising from the left posterior cerebral artery and solitary feeders arising from the posterior division of the left middle cerebral artery and pericallosal branch of the left anterior cere-



**Fig. 1.** Case 1 preoperative MRI. **a** T2-weighted axial image. **b** T2-weighted coronal image. **c** Postgadolinium T1-weighted sagittal image. Images show malformed, hypoplastic left parietal lobe with fairly extensive left hemispheric polymicrogyria and gliosis. Additional suspected focus of polymicrogyria and gliosis in the right parietal parasagittal region. Numerous prominent, serpiginous intracranial vessels, both arterial and venous, suggestive of congenital arteriovenous malformation are present. Case 1 preoperative angiogram. **d** AP view of left internal carotid artery injection.

**e** Lateral view of left internal carotid artery injection. Images show opacification of a pial fistula in the left parietal region, which is supplied by an enlarged posterior division branch of the left middle cerebral artery. There is opacification of the anterior branches and a second posterior division branch, which are diminutive in caliber. There are no definite normal branches of the left posterior cerebral artery. The fistula drains into a large varix, which subsequently drains into the superior sagittal sinus, at the lambdoid suture.

bral artery, which communicated through the venous varix to the midsuperior sagittal sinus (Fig. 1). These imaging findings further supported the results of the genetic analysis.

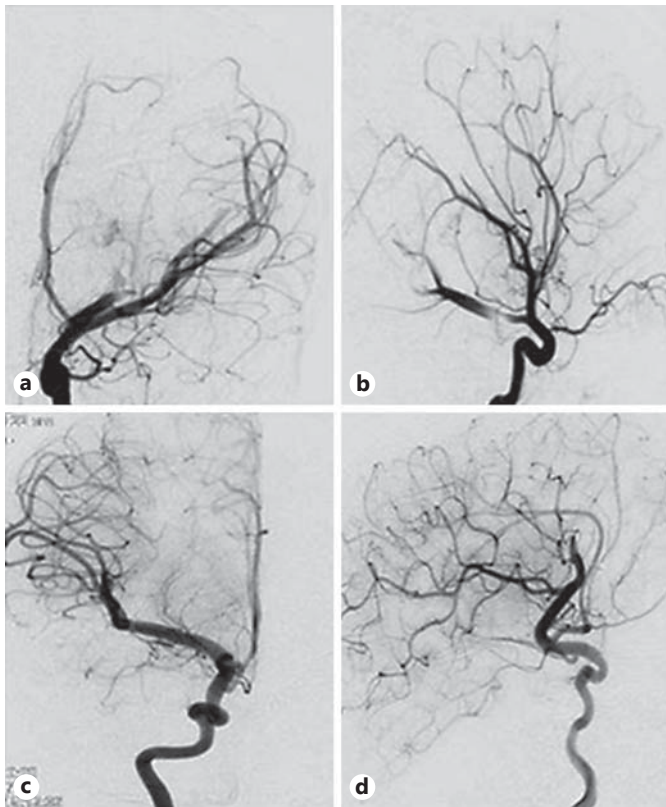
#### Operation and Postoperative Status

The patient underwent elective resection of the AVF. An occipital craniotomy was performed in the usual fashion for approach to the left supratentorial arteriovenous malformation with multiple arterial feeders. This vascular lesion was encountered after the dura mater was opened in a curvilinear fashion. CT angiographic images were used with frameless stereotactic computer-assisted navigation in planning for the craniotomy and approach to the arterial feeders of the malformation. Careful microdissection was performed to identify these feeders, which were found at the base of the malformation along with a large venous varix. Temporary clip occlusion was intermittently utilized along with final dissection around the aneurysm. There was an intraoperative rupture, which was controlled with clip occlusion. Overall, the patient

tolerated the procedure well. A subsequent CT scan of the head showed bilateral transverse right sigmoid and superior sagittal sinus thrombosis. However, a repeat angiogram several days later showed no filling of the fistula or early draining veins (Fig. 2a, b). He was discharged neurologically intact on a tapering dose of steroids and levetiracetam for seizure prophylaxis.

#### Follow-Up Evaluation

At the initial postoperative visit 1 month later, the patient was reported to be doing well with no seizure activity. An improvement in strength on the right side was noted as well. At a subsequent visit about 14 months postoperatively, the patient's status continued to improve and the mother reported that the child had been using his right hand more frequently for daily tasks. On examination, he was noted to have increased right hand grip strength. Follow-up MRI showed extensive cortical malformation and hypoplasia of the posterior aspect of the left cerebral hemisphere with resection cavity in the left parietal lobe. At the 4-year postoperative visit, he con-



**Fig. 2.** Case 1 postoperative angiogram. **a** AP view of the left internal carotid artery injection. **b** Lateral view of the left internal carotid artery injection. The images show no filling of AVF or early draining vein. Occlusion of the distal parietal branches of the anterior division of the left middle cerebral artery is noted in close proximity to previously clipped AVF with occlusion of the distal pericallosal branch of the left anterior cerebral artery in close proximity to the clipped AVF. Case 2 postoperative angiogram. **c** AP view of right internal carotid artery injection. **d** Lateral view of the right internal carotid artery injection. Total occlusion of the fistula and ICA bifurcation is seen. The right internal carotid artery opens into a hypertrophied right middle cerebral artery and right anterior cerebral artery. There is interval opacification of the right A1 segment with flash filling of the right anterior cerebral artery. The hypertrophied anterior M2 division tapers to complete occlusion.

continued to be neurologically stable. There were no further episodes of right-sided weakness, which may have been due to a steal phenomenon caused by high-flow pAVFs leading to a decrease in arterial supply along with underlying cortical pathology [4].

#### Case 2

##### History and Examination

This African-American female had initially presented at the age of 9 months to the pediatric ophthalmology department with progressive painless proptosis in the right eye. It was noted to be non-pulsating and nonerythematous. There was no history of visual

disturbances, diplopia, nausea, vomiting, lethargy, or focal neurological signs or symptoms. There had been no concern for seizures at this presentation. An outside hospital MRI showed abnormal vasculature in the right retro-orbital region. Upon follow-up MRA imaging and angiogram, the patient was found to have a pAVF arising from the right middle cerebral artery (Fig. 3). On examination, she had mild proptosis of her right eye and a slight prominence of the right maxilla. She was also noted to have multiple nonelevated, cutaneous, blanching vascular birthmarks on the abdomen, chest, and lower extremities. The rest of her physical examination was unremarkable. Of note, the patient's father had skin lesions clinically consistent with CMs. Subsequent genetic analysis revealed a mutation in the *RASA1* gene, confirming the link between the cutaneous lesions and the intracranial vascular malformations.

##### Operation and Postoperative Status

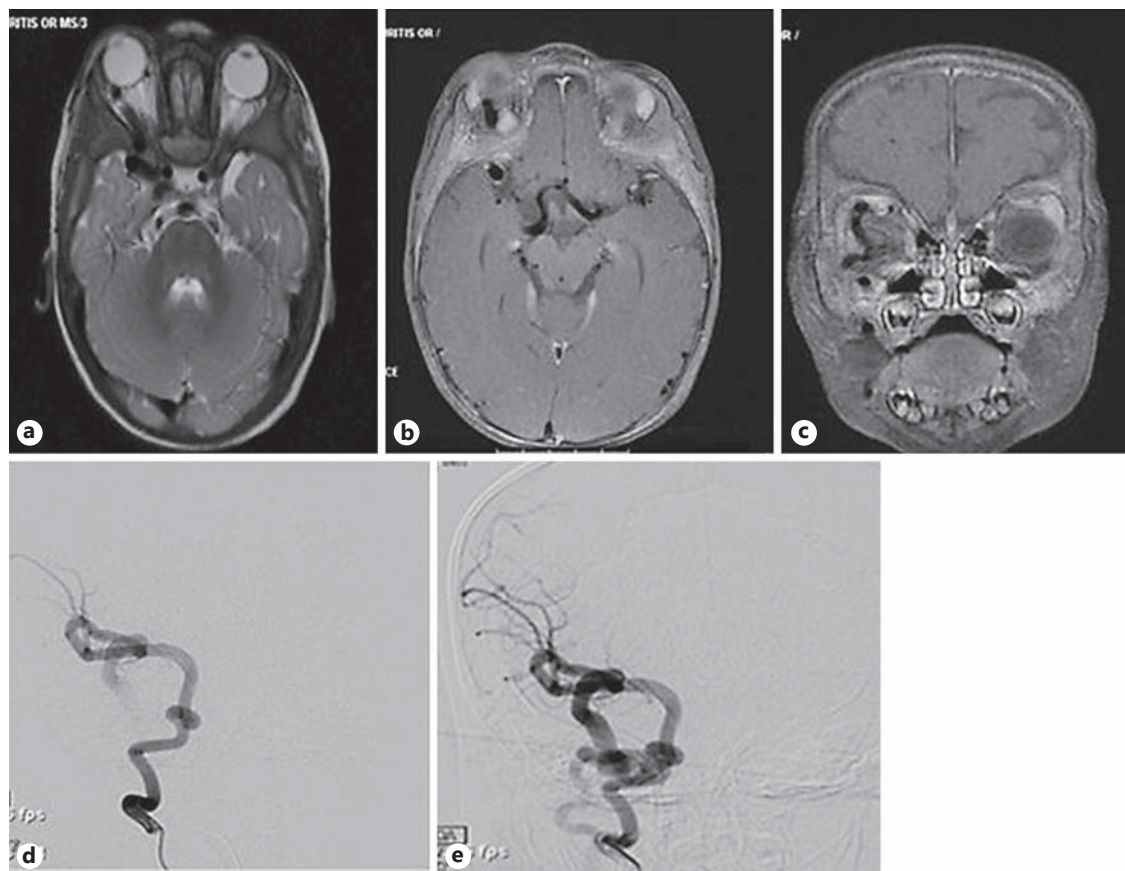
The patient underwent elective clipping of the right middle cerebral artery superior to the ophthalmic vein fistula. A pterional incision was outlined and carried down the bone. The bone was removed with a high-speed drill. The dura was incised in a curvilinear fashion and reflected anteriorly. The operating microscope was brought into position, and the sylvian fissure was dissected. The proximal middle cerebral artery was identified and the branches of the middle cerebral artery leading to the fistula site were identified. The fistula site was bulbous, and the arterialized vein was clearly identified heading toward the superior orbital fissure. A clip was placed along the connection between the artery and the vein, which provided near complete closure of the fistula. The patient tolerated the procedure well, and a postoperative CT scan revealed no evidence of acute intracranial hemorrhage. On postoperative day 1, she underwent an angiogram that was consistent with ligation of the fistula and appropriate filling of the right distal middle cerebral artery branches (Fig. 2c, d). At the time of discharge, she was awake and alert with no obvious neurologic deficit on examination.

##### Follow-Up Evaluation

The patient was seen 2 months postoperatively. There were no new residual deficits or worsening of proptosis of the right eye. On examination, she still had right-sided prominence of her orbit. In addition, she was noted to have an increase in the number of cutaneous, vascular lesions – especially on her face and abdomen. At a subsequent follow-up at the age of 20 months, the patient remained neurologically stable with no further progression of symptoms. Although the intraoperative assessment was a near-complete occlusion, follow-up angiograms demonstrated complete surgical obliteration of the fistula. Additionally, proptosis continued to improve with only a subtle enlargement present at the 4-year follow-up visit confirming complete occlusion.

## Discussion

CM presents as a characteristic macular stain with an incidence of 0.3% in neonates [5]. These are slow-flow lesions that consist of dermal capillary-like channels that are dilated and/or increased in number. Studies following families with such a phenotype have found that there is



**Fig. 3.** Case 2 preoperative MRI. **a–c** Scans of brain showing an enlarged right superior orbital vessel, dilated parasellar vessel, as well as a hypertrophied and tortuous right middle cerebral artery. The first 2 findings together would represent a caroticocavernous fistula on MRI. However, the involvement of a hypertrophic middle cerebral artery pointed to the rare diagnosis of a pial fistula to the enlarged right superior ophthalmic vein. Case 2 preoperative an-

giogram. **d** AP view of right internal carotid artery injection. **e** Lateral view of the right internal carotid injection. A hypertrophied and tortuous right middle cerebral artery is seen again anastomosing via a pial fistula to the enlarged right superior ophthalmic vein through the right facial vein ultimately into the right internal jugular vein. Again the right middle cerebral arteries and their branches opacify unremarkably.

an association between these cutaneous lesions and intracranial and extracranial AVMs and/or AVFs, which are considered fast-flow lesions. One study revealed that such fast flow lesions were found in the brain in 7.8% of cases, face in 7.8%, and limbs in 3.6%. Subsequent genetic testing in these patients revealed heterozygous mutations in the *RASA1* gene and, hence, the recently described clinical entity of CM-AVM was defined. Heterozygous mutations occurring in the *RASA1* gene can disrupt the normal proliferation of endothelial cells into highly organized networks. Furthermore, studies have found that this gene performs a critical effector function downstream of the endothelial receptor *EPHB4*, which modulates activity of mTORC1. In zebrafish models, deficiencies in either *RASA1* or *EPHB4* induced overactivation of mTORC1,

producing strikingly similar abnormalities in blood vessel formation and function. In addition, tissue samples from patients with AVMs increased mTORC1 activity [6]. An anecdotal study found that murine embryos deficient in this particular gene had early developmental arrest due to severe vascular defects [7].

CM-AVMs have gained recent popularity as intracranial vascular lesions associated with a rather common cutaneous vascular anomaly. Interestingly, the cutaneous capillary stains present in patients with this mutation appear slightly different than the common variety CM. Small, usually multifocal and randomly distributed CMs are more characteristic of this disease entity. CMs per se are present in several different clinical syndromes such as Sturge-Weber, Klippel-Trenaunay, and Parkes Weber [5,

8, 9]. A couple of studies, which followed 17 and 42 families, respectively, documented that heterozygous mutations in this particular gene results in multifocal CMs in all individuals studied but also noted the presence of either AVMs (intra- and extracranial), AVFs, or Parkes Weber syndrome in all of the families. The prevalence of the former two occurring in conjunction with cutaneous CMs is anywhere in the range of 15–20% [5, 10].

Conventional catheter angiography (CCA) is the current reference standard for the diagnosis, assessment, and management of brain pAVMs. Conventional MRI/MRA or CTA examinations may also be used as initial forms of investigation but are not ideal for the detection of such anomalies, especially smaller AVMs. Studies have also experimented with assessment via dynamic MR digital subtraction angiography (DSA). In one particular study, the rate of detection of intracranial AVMs via DSA was 19 out of 20 patients, and correlation with CCA was excellent for measurements of maximum diameter [11]. To expand on the use of DSA, identification of venous signal on arterial spin labeling (ASL) is thought to improve upon the diagnosis of smaller AVMs. In a study of 26 patients, the rate of agreement among neuroradiologists in predicting positive findings was significantly improved with the use of venous ASL [12].

The discovery of *RASA1* mutations in patients with CMs and the recognition of the resulting clinical entities – CM-AVMs and pAVFs – has greatly expanded our knowledge on genetic associations of pediatric craniofacial vascular lesions. In the setting of characteristic multifocal CMs with or without known AVMs, clinicians should include *RASA1* mutation in the differential diagnosis due to the high degree of association between intracranial vascular malformations and cutaneous vascular lesions. Brain imaging should be obtained to identify AVMs/AVFs to ideally allow for early detection and intervention prior to development of symptoms [10]. Although there is no consensus in the literature regarding imaging of the spine in these patients, studies have reported an association between this mutation and spinal AVMs [2]. In addition, further extracranial imaging may be needed especially in cases of cardiac failure where AVM/AVF may be the etiology [5, 13]. Thus, the threshold for further investigation should be lowered as compared to the general population.

We recommend genetic testing when clinical suspicion is high. Sequence analysis can detect small intragenic deletions/insertions, missense, nonsense, and splice-site mutations. Deletions/duplications not picked up by routine sequencing can be detected by PCR, multiplex

ligation-dependent probe amplification, and chromosomal microarray. Chromosomal microarray was used in both of our patients. Considering that *RASA1*-related disorders are generally inherited in an autosomal dominant manner, testing should also be recommended for other family members – in particular, at-risk infants should be tested for immediate diagnosis. Both of our patients appeared to have inherited mutations but de novo mutations do occur approximately 30% of the time [10].

Treatment of pAVF can be a technically difficult procedure due to absence of a nidus. Treatment must be performed with surgical or endovascular obliteration of the fistulas at the point of AV connection; adjunct embolization using liquid embolic agents can also be used prior to surgery. The decision to use a surgical or endovascular approach is dependent on the size and eloquence of neighboring brain tissue. Conventional clipping or cauterization are effective, but carry a high mortality risk if the lesions are deep-seated or located in eloquent areas. Endovascular approaches avoid some of the risks associated with surgery and can reduce posttherapeutic hyperemia, but are limited by angiometric configuration, and access may be difficult due to multiple arterial connections [14, 15]. Regardless of the treatment modality chosen, the ultimate goal is complete occlusion to prevent long-term recurrence. Long-term surveillance data on this entity is limited, but recurrence has certainly been hypothesized in the literature [16]. As stated above, threshold of further imaging should be kept low [17].

Pertinent to our study, management can be quite difficult particularly in regards to neonatal pAVF. Endovascular embolization may be an appropriate form of treatment in older children (>2 years of age) who tend to present with single-hole arteriovenous shunts as opposed to the multiple arteriovenous shunts present in children <2 years, which can require a multitude of embolizations [3]. Because of the differing clinical presentations, the goal of treatment in these older children is directed at preventing chronic cerebral venous HTN as opposed to preventing CHF in younger children. In our patients, challenges to the endovascular approach included the presence of a high-flow fistula, tortuous intracranial feeding arteries, and limitations in the volume of contrast that could be used. Although the vasculature in case 2 (Fig. 3) does not appear to be extremely tortuous, intraoperative reports confirmed the tortuosity of the vessels. Stereotactic radiosurgery is another option that may be recommended for patients with pAVF who also have an AVM nidus. This was not done in patient 1 presumably due to reduced efficacy in inducing regression of large-caliber fistulas. Re-

regardless of intervention choice, postoperative complications can include hydrocephalus, likely related to venous thrombosis of often markedly patulous veins or possibly related to impaired venous outflow with altered CSF dynamics. In general, clinical outcomes are dependent on the complexity of the initial lesions and the age of presentation. The more complex or the higher number of AVFs present can lead to a greater chance of developing CHF. Because these tend to occur in children younger than 2, poorer prognosis is conferred in this patient population as opposed to older children.

## Conclusions

Pial AVFs and CM-AVMs have recently been identified as categories of intracranial vascular pathologies similar to AVMs, cavernomas, and telangiectasias. In patients with noted skin CM, especially when atypical in presentation and associated with neurological signs and

symptoms (headache, macrocrania, seizures, and focal weakness), the possibility of intracranial or spinal fast flow lesions should be considered. Genetic screening for *RASA1* along with other known associated syndromes, such as hereditary hemorrhagic telangiectasia, would appear to be indicated. Treatment is effective in the obliteration of these high-flow lesions, and in a great majority of patients, results in excellent outcomes.

## Ethics Statement

Not applicable. The anonymous information presented does not lend itself to a need for any subject to give his or her informed consent, nor is the information part of any study protocol requiring approval by our institute's committee on human research.

## Disclosure Statement

The authors declare no conflicts of interest.

## References

- 1 Walcott BP, Smith ER, Scott RM, Orbach DB: Pial arteriovenous fistulae in pediatric patients: associated syndromes and treatment outcome. *J Neurointerv Surg* 2013;5:10–14.
- 2 Thiex R, Mulliken J, Revencu N, Boon L, Burrows P, Cordisco M, Dwight Y, Smith E, Vikkula M, Orbach D: A novel association between *rasa1* mutations and spinal arteriovenous anomalies. *AJNR Am J Neuroradiol* 2010;31:775–779.
- 3 Hettis S, Keenan K, Fullerton H, Young W, English J, Gupta N, Dowd C, Higashida R, Lawton M, Halbach V: Pediatric intracranial nongalenic pial arteriovenous fistulas: clinical features, angioarchitecture, and outcomes. *AJNR Am J Neuroradiol* 2012;33:1710–1719.
- 4 Aziz-Sultan MA, Elhammady MS, Heros RC: Surgical approaches and nuances for supratentorial arteriovenous malformations. *Comp Manag Arterio Malf Br Sp* 2014, p 113.
- 5 Eerola I, Boon LM, Mulliken JB, Burrows PE, Domp Martin A, Watanabe S, Vanwijck R, Vikkula M: Capillary malformation-arteriovenous malformation, a new clinical and genetic disorder caused by *rasa1* mutations. *Am J Hum Genet* 2003;73:1240–1249.
- 6 Kawasaki J, Aegerter S, Fevurly RD, Mammoto A, Mammoto T, Sahin M, Mably JD, Fishman SJ, Chan J: *RASA1* functions in EPHB4 signaling pathway to suppress endothelial mTORC1 activity. *J Clin Invest* 2014;124:2774.
- 7 Henkemeyer M, Rossi DJ, Holmyard DP, Puri MC, Mbamalu G, Harpal K, Shih TS, Jacks T, Pawson T: Vascular system defects and neuronal apoptosis in mice lacking *ras* GTPase-activating protein. *Nature* 1995;377:695–701.
- 8 Duffy K: Genetics and syndromes associated with vascular malformations. *Pediatr Clin North Am* 2010;57:1111–1120.
- 9 Hershkovitz D, Bercovich D, Sprecher E, Lapidot M: *RASA1* mutations may cause hereditary capillary malformations without arteriovenous malformations. *Br J Dermatol* 2008;158:1035–1040.
- 10 Revencu N, Boon LM, Mulliken JB, Enjolras O, Cordisco MR, Burrows PE, Clapuyt P, Hammer F, Dubois J, Baselga E: Parkes Weber syndrome, vein of Galen aneurysmal malformation, and other fast-flow vascular anomalies are caused by *rasa1* mutations. *Hum Mutat* 2008;29:959–965.
- 11 Griffiths PD, Hoggard N, Warren DJ, Wilkinson ID, Anderson B, Romanowski CA: Brain arteriovenous malformations: assessment with dynamic MR digital subtraction angiography. *AJNR Am J Neuroradiol* 2000;21:1892–1899.
- 12 Le T, Fischbein N, Andre J, Wijman C, Rosenberg J, Zaharchuk G: Identification of venous signal on arterial spin labeling improves diagnosis of dural arteriovenous fistulas and small arteriovenous malformations. *AJNR Am J Neuroradiol* 2012;33:61–68.
- 13 Durrington HJ, Firth HV, Patient C, Belham M, Jayne D, Burrows N, Morrell NW, Chilvers ER: A novel *RASA1* mutation causing capillary malformation-arteriovenous malformation (CM-AVM) presenting during pregnancy. *Am J Med Genet A* 2013;161:1690–1694.
- 14 Yamashita K, Ohe N, Yoshimura S, Iwama T: Intracranial pial arteriovenous fistula-case report. *Neurol Med Chir (Tokyo)* 2007;47:550–554.
- 15 Chaudhary N, Gemmete JJ: Endovascular Management of Neurovascular Pathology in Adults and Children, an Issue of Neuroimaging Clinics. Amsterdam, Elsevier Health Sciences, 2013.
- 16 Orme CM, Boyden LM, Choate KA, Antaya RJ, King BA: Capillary malformation-arteriovenous malformation syndrome: review of the literature, proposed diagnostic criteria, and recommendations for management. *Pediatr Dermatol* 2013;30:409–415.
- 17 Bayrak-Toydemir P, Stevenson D: *RASA1*-related disorders (February 22, 2011; updated December 19, 2013); in Pagon RA, Adam MP, Ardinger HH, et al (eds): GeneReviews (Internet). Seattle, University of Washington, 1993–2015.