ORIGINAL RESEARCH

Pial arteriovenous fistulae in pediatric patients: associated syndromes and treatment outcome

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ABSTRACT

Objective Pediatric pial arteriovenous fistulae (pAVF) are rare vascular lesions of the CNS, reported to have up to a 25% association with hereditary hemorrhagic telangiectasia. The presentation, treatment and syndromes associated with pAVF in children are reported here.

Design A pediatric database for pAVF was retrospectively reviewed. Patients with carotid–cavernous fistulae, dural arteriovenous fistulae, brain arteriovenous malformations and vein of Galen malformations were excluded. Radiographic outcome was assessed using digital subtraction angiography, and clinical outcome by the Functional Status Scale (6=normal, maximal incapacity=30).

Results Between July 2003 and June 2011, seven patients with pAVF (six intracranial and one spinal) were treated. Mean age was 4.2 years. The most common clinical presentation was high output cardiac failure (43%). Two patients (29%) harbored a known mutation in the RASA1 gene, associated with a hereditary vascular syndrome: capillary malformation–arteriovenous malformation. No patient had hereditary hemorrhagic telangiectasia. Treatment resulted in complete lesional obliteration in six of seven patients, with treatment ongoing in the seventh. Five of seven patients had combined endovascular and surgical treatment while two underwent endovascular embolization alone. Functional Status Scale scores at the most recent follow-up were 6 in all but one patient who had presented with a pretreatment hemianopsia.

Conclusion Treatment is effective in obliterating pAVF in children, with an excellent prognosis seen in our cohort. Genetic screening is indicated, with capillary malformation–arteriovenous malformation being the most frequently seen syndrome. No patients had hemorrhagic hereditary telangiectasia.

INTRODUCTION

Pediatric pial arteriovenous fistulae (pAVF) are rare vascular lesions of the CNS, characterized by direct arterial connections to a pial venous channel, without an intervening nidus.[1] The most common clinical presentations in children are cardiac insufficiency, epilepsy and macrocrania.[2] In previous retrospective series of pAVF, an association (up to 25%) with hereditary hemorrhagic telangiectasia (Online Mendelian Inheritance in Man No 187300) has been reported.[2 3] Treatment of pAVF can be microsurgical, endovascular or combined, depending on clinical and angiographic factors. We reviewed data from our high volume pediatric cerebrovascular center to determine presentation, treatment outcomes and syndromes associated with pAVF.

MATERIALS AND METHODS

Institutional review board approval was granted for this retrospective study. We searched the Children's Hospital neurosurgical and neurointerventional databases and identified patients treated for pAVF, which are characterized by direct arteriovenous shunting from a pial arterial source(s) to a pial vein, without intervening nidus. Patients with carotid–cavernous fistulae, dural arteriovenous fistulae, brain arteriovenous malformations and vein of Galen malformations were excluded. Radiographic outcome was assessed using digital subtraction angiography, and clinical outcome by the Functional Status Scale.[4]

RESULTS

Between July 2003 and June 2011, seven patients with pAVF were treated, with a mean age at presentation of 4.2 years (table 1); by way of comparison, during this same time period, 58 patients with brain arteriovenous malformations (AVM) and eight patients with dural arteriovenous fistulae were treated by our group. In the cohort of three females and four males with pAVF, the most common clinical presentation was high output cardiac failure (three patients), followed by hemorrhage and headache in one patient each. Two patients had asymptomatic lesions and were diagnosed on screening examination.

Two of seven (29%) patients had capillary stains of the skin, with first degree relatives harboring similar lesions (figures 1 and 2). Genetic screening demonstrated both of these patients to have a known mutation in the RASA1gene, associated with a recently described syndrome, capillary malformation–arteriovenous malformation (CM-AVM) (OMIM No 608354). A third patient had numerous capillary malformations of the skin but did not harbor any of the known mutations in the RASA1 gene; this patient was adopted and whether first degree relatives also harbored capillary malformations was unknown. No patient in our cohort of pAVF had hereditary hemorrhagic telangiectasia, based on genetic testing, clinical presentation and family history.[5]

Treatment resulted in complete lesional obliteration in six of the seven patients, with treatment ongoing in the seventh. Five of seven patients had combined endovascular and surgical treatment, while two underwent endovascular embolization alone. Functional Status Scale scores at a mean follow-up of

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Table 1 Patient characteristics

Patient No	Age (years)	Treatment	Presentation	Complication	Angiographic outcome	FSS score	Vascular syndrome	Follow-up (months)
1	7	Partial embolization, emergent craniotomy	Intracranial hemorrhage	None	Complete	6	None	31
2	14	Balloon test occlusion, elective craniotomy	Headache	None	Complete	6	None	7
3	0.2	Embolization of main fistula, craniotomy × 2	High output cardiac failure	None	Complete	6	None	12
4	0.1	Embolization, craniotomy, ventriculostomy	High output cardiac failure	Hydrocephalus	Complete	7 (hemianopsia)	None	12
5	0.1	Staged embolization (2 rounds)	Cranial bruit	None	Residual	6	CM-AVM (RASA1+)	4
6	5	Preoperative embolization, open surgery	Headache, history of foot arteriovenous malformation	None	Complete	6	CM-AVM (RASA1+)	30
7	3	Embolization	Seizure workup	None	Complete	6	None	2

CM-AVM, capillary malformation–arteriovenous malformation; FSS, Functional Status Scale; RASA1, RAS p21 protein activator 1 (cytogenetic location 5q13.3).

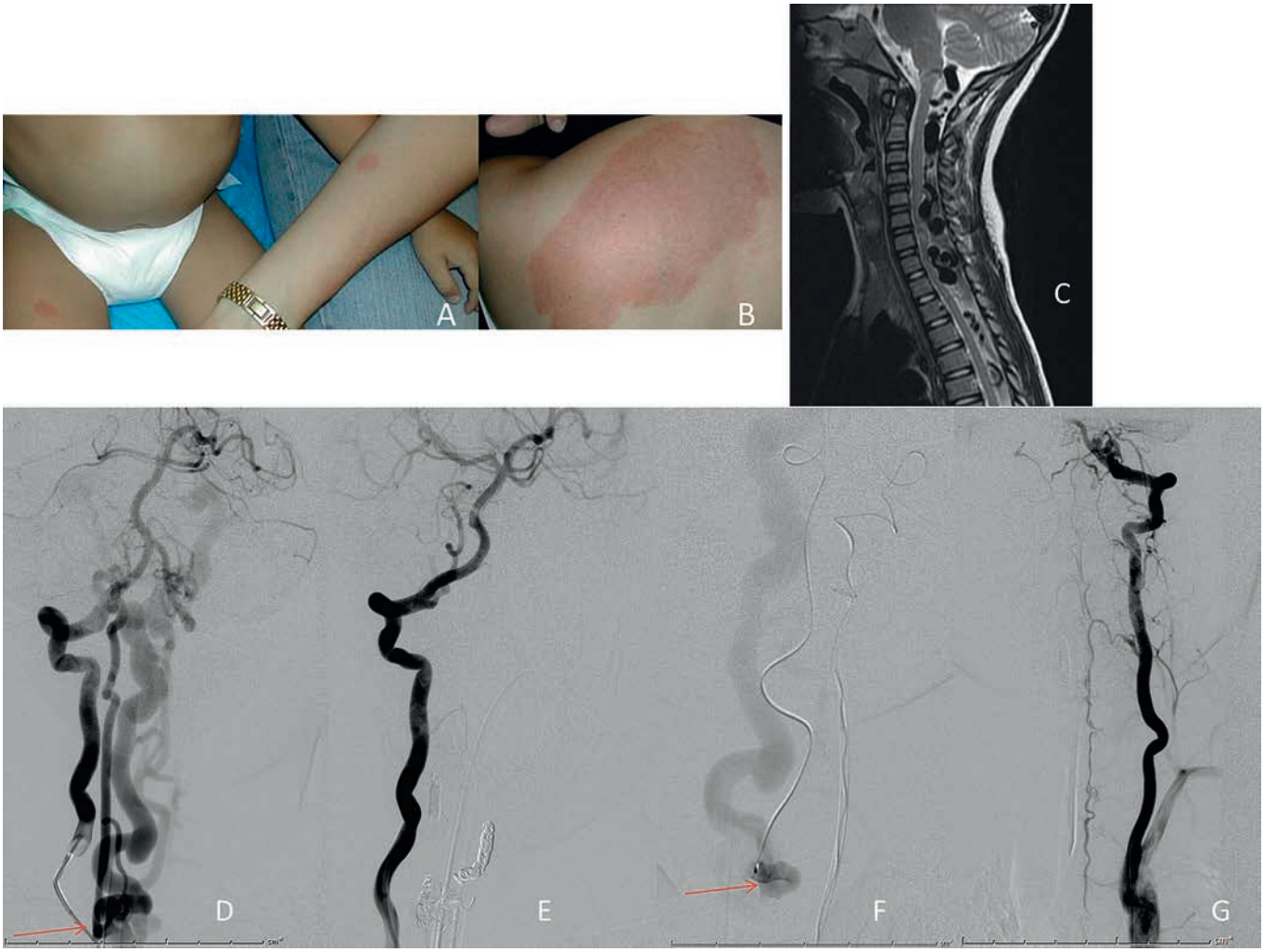

Figure 1 A patient with capillary malformation–arteriovenous malformation (CM-AVM) with a spinal pial fistula. (A) The patient's right thigh skin stain photographed with his mother's left forearm. (B) A larger capillary malformation on the mother's upper back. (C) Sagittal view of a T2 weighted image of the cervical spine showing massively dilated intradural vessels from the cervicomedullary junction to the mid-thoracic spine, suggestive of a high flow arteriovenous lesion. (D) Frontal view of a right vertebral artery injection, showing an enlarged right posterior spinal artery supplying a direct fistula at the level of C7/T1 (red arrow). (E) Frontal view of a right vertebral artery injection after coil embolization of the right posterior spinal artery supply. (F) Frontal view of a microcatheter injection in the distal left posterior spinal artery, illustrating the direct fistulous inflow into the venous pouch (red arrow), a mirror image of the right side. Additional tortuous supply to the fistula via the anterior spinal arterial axis is not shown but definitive treatment necessitated surgical resection of the venous pouch. (G) Postoperative injection of the left vertebral artery showing no residual arteriovenous shunting, with a patent anterior spinal axis.

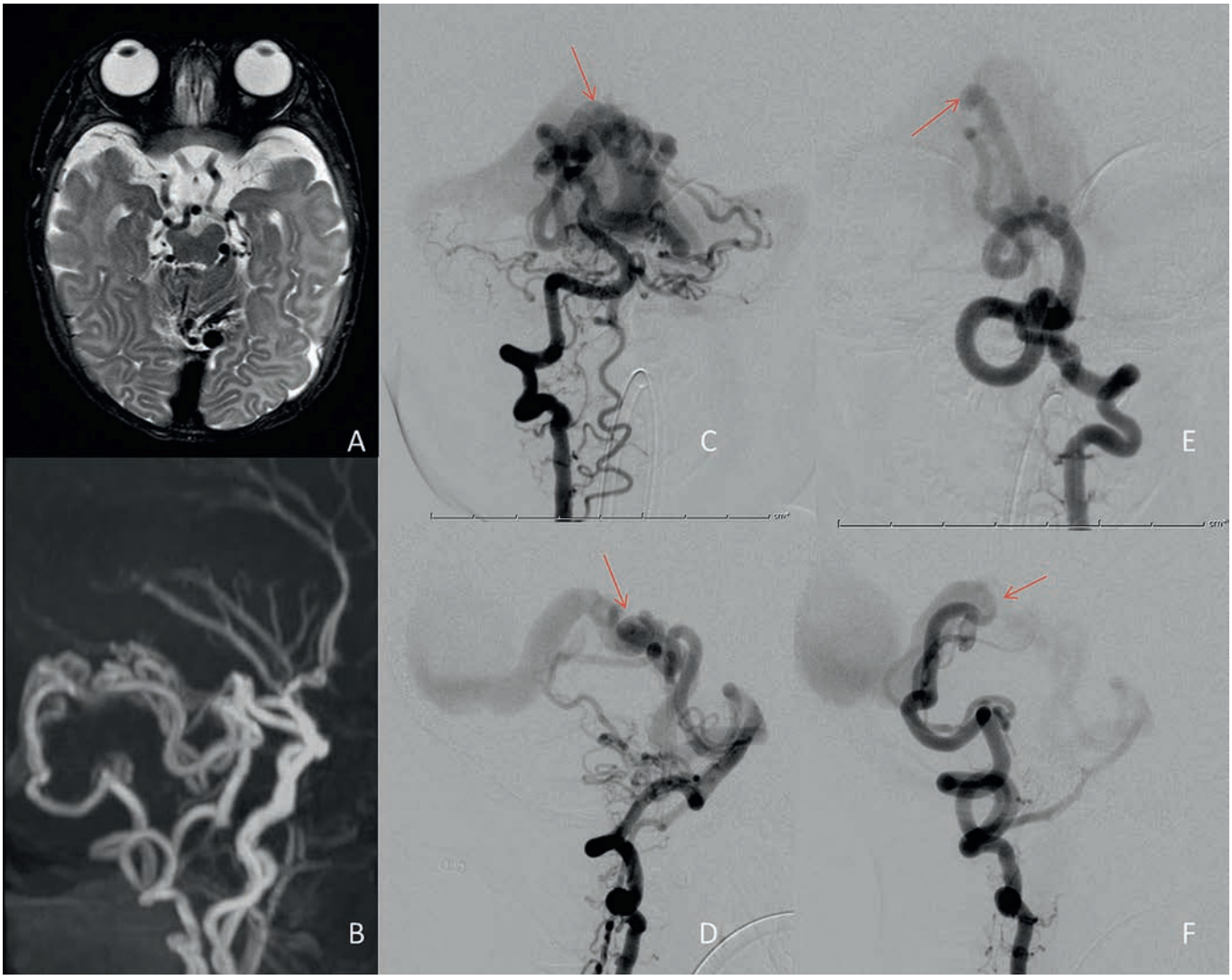

Figure 2 Two-month-old infant with capillary malformation—arteriovenous malformation (CM-AVM) and posterior fossa pial fistula. (A) Axial T2 weighted image showing enlarged flow voids in the quadrigeminal plate and superior vermian cisterns flowing into a massively enlarged torcular. (B) MR angiography maximum intensity projection lateral view showing enlarged posterior inferior cerebellar and superior cerebellar arterial branches providing inflow to an arteriovenous fistula converging in the region of the superior vermian cistern, as expected with a high flow arteriovenous lesion. (C) Frontal and (D) lateral views of a right vertebral artery injection showing enlarged bilateral superior cerebellar supply to a high flow arteriovenous fistula. Red arrows show the fistulous inflow to the venous collector. (E) Frontal and (F) lateral views of a left vertebral artery injection showing enlarged and markedly tortuous left posterior inferior cerebellar inflow into the fistula, at a point slightly more posterior on the venous collector than that seen with the right-sided injection.

16 months, assessing mental status, sensory functioning, communication, motor functioning, feeding and respiratory status, each on a scale from 1–5, were 6 (normal for age) in all but one patient who had presented with a pretreatment hemianopsia.

Clinical vignette

A 14-year-old female presented for evaluation following neuroimaging in the context of headache. On brain MRI, she was found to have a prominent left middle cerebral artery branch and venous ectasia suggestive of pAVF. Diagnostic cerebral angiography demonstrated a focal arteriovenous fistula involving a single middle cerebral artery superior division branch feeding directly into an ectatic and tortuous left cerebral hemispheric vein, with tributaries draining into the superior sagittal sinus and left transverse sinus. The initial plan was to use endovascular means to obliterate the fistulous connection but angiographic balloon test occlusion revealed prominent arterial branches originating near the fistulous communication, supplying normal (and likely eloquent) left parietal brain parenchyma (figure 3). The decision was made to proceed with microsurgical obliteration of the lesion to mitigate the risk of non-target embolization. A craniotomy was performed and a superficial temporal artery graft was prepared for potential use for extracranial to intracranial bypass. With the malformation exposed, an indocyanine green dye angiogram was performed with an 800 nm wavelength optical detector (Infrared 800, Opmi Pentero, Carl Zeiss, Germany). An aneurysm clip was applied to the fistulous connection and a second indocyanine green dye study performed, demonstrating no flow through the fistula. Excellent opacification of the arterial branches that lay in close proximity to the fistulous connection was seen, and the superficial temporal artery graft was not needed. Immediate postoperative digital subtraction angiography demonstrated complete obliteration of the fistulae and preservation of flow otherwise (figure 3). The patient recovered with no neurological deficit.

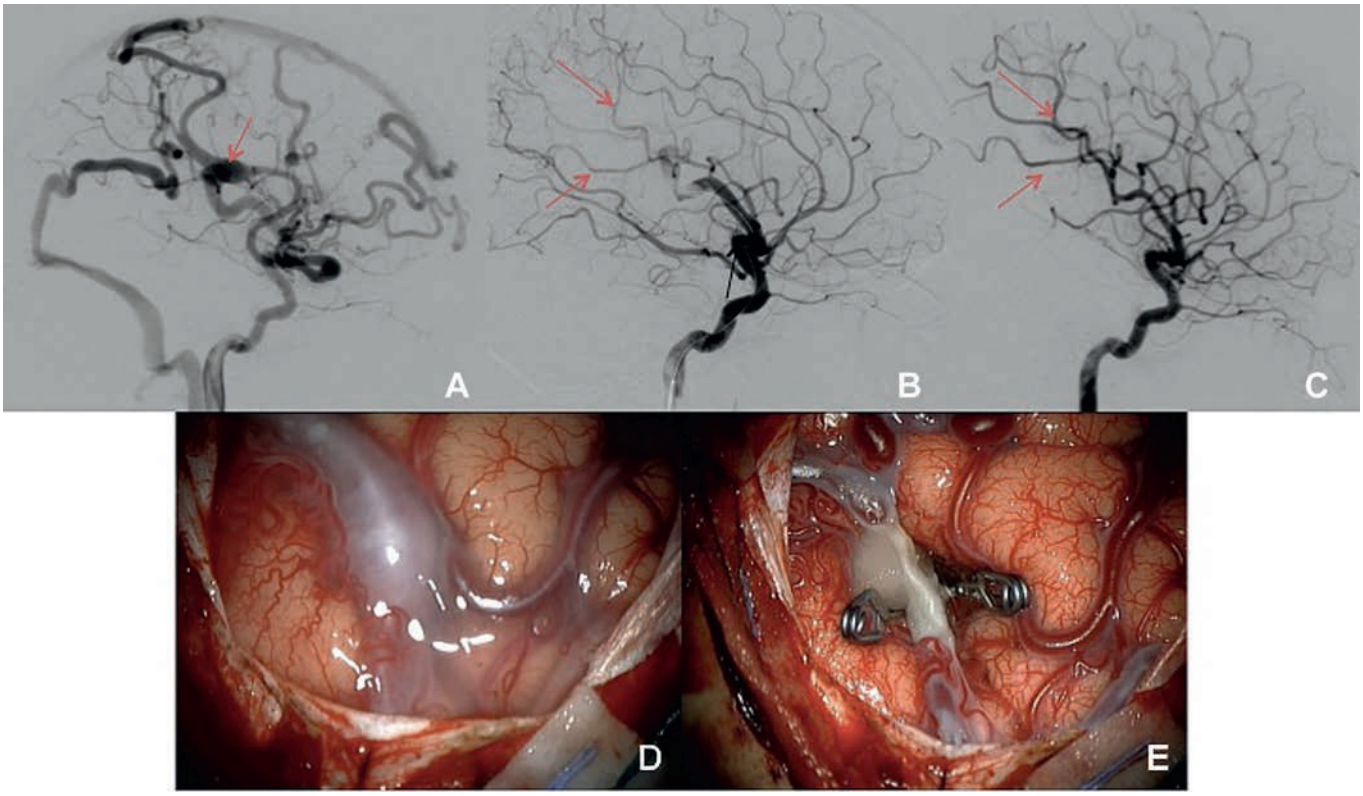

Figure 3 Single hole pial arteriovenous fistula arising from the superior division of the left middle cerebral artery (MCA). (A) Lateral view of a left internal carotid artery injection, mid-arterial phase, showing a single hole arteriovenous fistula (red arrow at fistulous connection), with the venous collector in turn demonstrating multidirectional intracranial pial venous outflow and pressurization over the left hemisphere. (B) Lateral view, left internal carotid artery injection, mid-arterial phase, with a balloon inflated just proximal to the fistulous point (black arrow indicating the filling defect due to the balloon). With flow through the fistula occluded, the MCA candelabra is now seen, and two parietal branches originating adjacent to the fistulous point are now seen (red arrows), prompting the decision to treat the patient with open surgical disconnection of the fistula. (C) Lateral view, left internal carotid artery injection, mid-arterial phase, postoperative angiogram. No early venous opacification is seen. The two left MCA branches identified on balloon occlusion of the fistula remain patent (red arrows). Intraoperative images demonstrating the arteriovenous fistulae on the cortical surface before (D) and after (E) surgical obliteration with clipping. Note the deflation of the fistula.

DISCUSSION

Pial arteriovenous fistulae are rare lesional vascular anomalies that pose a high risk of intracranial hemorrhage across all age groups, including children.[6] In the pediatric population in particular, they may present with high output cardiac failure,[2 7 8] macrocrania, seizures or with large venous varices[9] exerting a mass effect. In infants, an audible murmur or cranial bruit is occasionally heard, secondary to the high flow.[10]

Aberrations in blood vessel formation and segregation during embryonic development are thought to be responsible for the development of these lesions[11] although the process by which this abnormal arteriovenous communication occurs is poorly understood. Early fate mapping studies in zebrafish have shown that arterial or venous identity is acquired early as a result of genetic determination,[12] initiated by molecular signals that result in functional and subsequently structural changes.[13 14] However, several hierarchical signaling pathways have been found to promote or inhibit divergent endothelial cell fates, including Hedgehog, vascular endothelial growth factor, Notch, chicken ovalbumin upstream transcription factor II and the ephrin ligand–receptor pathway.[15] Of these, the ephrin ligand–receptor pathway, originally identified in the study of neuronal pathfinding,[16] has been implicated as a crucial regulator of vascular assembly, differentiation and boundary formation. It is thus likely that the interplay of several parallel and convergent signaling pathways is involved in the development of congenital pathological fistulous vascular connections.

The treatment of pAVF involves endovascular and microsurgical techniques to close the fistulous connection. Given their rarity, overall experience with treating pediatric patients is limited.[2 7 8 17 18] Surgical treatment remains an option in some cases, particularly when risk of non-target embolization to eloquent brain cortex is high.[19] Following treatment, patients should be monitored for the development of hydrocephalus, related perhaps to venous thrombosis of often markedly patulous veins or possibly related to impaired venous outflow with altered CSF dynamics. In a series of 16 patients treated endovascularly, nearly 19% experienced post-procedure hydrocephalus.[20] A single patient in our series also developed hydrocephalus, the etiology of which was unclear.

It has been previously reported that patients with pAVF have a frequent association with hemorrhagic hereditary telangiectasia (HHT).[2 3] However, the diagnosis of HHT is rarely made based on genetic testing, relying instead on clinical findings often absent in young children (such as recurrent epistaxis, mucocutaneous telangiectasias and non-CNS arteriovenous lesions) and a family history of such clinical findings; the constellation of diagnostic criteria for HHT are known as the 'Curacao criteria'.[21] The association between HHT and pAVF was similarly based on such clinical grounds. However, recently, mutations in the RASA1 gene have been found to be associated

with a novel clinical entity, CM-AVM,[22] in which patients with numerous skin capillary stains (and frequently with a family history of such skin stains) have peripheral, brain[23] and spinal[24] arteriovenous lesions. It may very well be the case that in studies predating the identification of RASA1, patients were mistakenly classified as having HHT on purely clinical grounds. Indeed, we identified a known RASA1 mutation in two of seven patients in our cohort (29%) (figures 1 and 2). A third patient had skin lesions quite characteristic of CM-AVM but did not harbor one of the known mutations; it is certainly possible that additional mutations of the RASA1 gene will be discovered to be associated with the clinical syndrome.

Although mistaken conflation of RASA1 patients with HHT may underlie some reports regarding pAVF in the older literature, it remains striking that none of the seven patients in our cohort had genetic results, clinical history or a family history suggestive of HHT.[5 25] One possible explanation for this may be related to a population sampling anomaly: our center is geographically close to a medical center which is a major HHT treatment hub. It may thus be the case that patients referred to us were systematically undersampled with regard to HHT prevalence.

The issue of how and whether to treat patients with asymptomatic pAVF has not been well elucidated; certainly, results from conservative management in any such cohort have not been described. With regard to HHT, there are several case reports of patients who harbored cerebral arteriovenous shunts that underwent spontaneous regression.[26–28] However, all of our patients presented symptomatically, while none had HHT, as mentioned.

Given the association suggested in our cohort between CM-AVM and pAVF, we recommend that the presence of a CNS arteriovenous fistula, in particular in association with skin capillary malformations, should prompt a genetic investigation for RASA1 mutation.

CONCLUSION

Pial arteriovenous fistulae are rare vascular lesions of the CNS in children that may present with cardiac failure, intracranial hemorrhage, seizures, mass effect or macrocrania. Treatment, endovascular and/or surgical, is effective in the obliteration of these high flow lesions, and in the great majority results in excellent outcomes. No patient in our cohort had HHT based on the Curacao criteria or genetic testing, while there was a high incidence of RASA1 mutations and phenotype in our cohort. However, given the previously known association between pAVF and HHT, genetic screening for both HHT and RASA1 would appear to be indicated.

Competing interests None.

Ethics approval The study was approved by the Children's Hospital Boston institutional review board.

Contributors BPW performed the database analysis and wrote the first draft. ERS, RMS and DBO participated in the discussions around the project, contributed intellectual content and edited the manuscript.

Provenance and peer review Not commissioned; externally peer reviewed.

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