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Nocturnal Headaches and Pulsatile Cranial Mass: The Tip of an Iceberg

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Abstract

BACKGROUND—Capillary malformation-arteriovenous malformation (CM-AVM) disorder is a newly defined hereditary disorder of the vasculature with typical defining features that include cutaneous capillary malformations associated with high-flow lesions in various other organ systems. Mutations on the RASA1 gene are reported to be associated with a variety of vascular malformations and present with a widely varying phenotype.

PATIENT—A healthy 3 year old presented with acute onset of severe nocturnal headaches, nausea, and vomiting associated with a 2-cm pulsatile mass and prominent superficial veins on her forehead. Neuroimaging demonstrated a complex vascular malformation with multiple arteriovenous fistulae and cavernous angiomas present in multiple locations in the brain, but not in any other organ system.

RESULTS—The patient was found to have a mutation of the RASA1 gene, which has not been previously described in the literature.

CONCLUSIONS—This case describes a new RASA1 mutation with a phenotype that has not been previously described with a combination of pial fistulae and intracranial AV fistula in the absence of arteriovenous malformations.

Introduction

RAS p21 protein activator (RASA1) gene-related disorders are usually associated with capillary malformations with or without arteriovenous (AV) malformations or AV fistulas. We are reporting novel case of a 3-year-old patient with a novel case of a RASA1 gene variant who was found to have multiple AV fistulas and cavernous angiomas in the absence of capillary malformations.

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Case Report

A 3-year-old female presented with the sudden onset of severe nocturnal headaches associated with nausea and vomiting. The child's mother reported a newly formed, nontender, pulsatile mass on the left frontal region. Physical examination demonstrated a 2-cm pulsatile mass protruding through the skull and prominent superficial veins on her forehead. A harsh bruit was audible on auscultation of her head, but no heart murmur was present. Neurologic examination was unremarkable.

Urgent brain magnetic resonance imaging with arteriography and venography showed a complex vascular malformation with multiple AV fistulae (AVF) and cavernous angiomas in the frontal lobe, in the left thalamic areas, and in the cerebellar hemisphere on the left side (Fig 1). The AVF were supplied anteriorly by the ophthalmic and maxillary arteries and by a severely hypertrophic middle meningeal artery (Fig 2) and posteriorly by multiple arterial branches (posterior cerebral artery, superior cerebellar artery, and vertebral artery branches). Final drainage was into a severely dilated superior sagittal sinus via a persistent falcine sinus. The superficial and deep venous system was markedly dilated mainly at the superior sagittal sinus, transverse and straight sinuses, and at the level of the vein of Galen. Focal narrowing was noted at the jugular bulb bilaterally, suggesting constriction of outflow. No additional vascular abnormalities were identified in other organs by chest computed tomography and liver and kidney ultrasounds. Bidirectional genetic sequencing of the RASA1 gene identified a heterozygous gene missense mutation (c.2084A>T; p.His695Leu) not previously reported. Parental testing was performed on the asymptomatic mother and confirmed the presence of the same mutation. However, because reduced penetrance of RASA1-related disorders has been described,² this finding could not rule out a causal relationship between the mutation and the clinical findings.

Over the following year, despite repeated embolization procedures to diminish flow in the various AV fistulae, the patient continued to develop new AV connections. Repeated studies demonstrated relentless disease progression with enlargement of previously embolized vessels and reestablishment of AV flow. She suffered recurrent micro-hemorrhages around the thalamic cavernous angioma. In time, she developed obstruction of the venous outflow with stenosis and ultimately occlusion of the left jugular bulb leading to increased intracranial pressure nonresponsive to medical treatment that resulted in death.

Discussion

CM-AVM disorder is a relatively newly discovered disorder defined by the formation of cutaneous capillary malformations in addition to high-flow AV lesions and AVF in multiple organs.¹ CV-AVM disorder is caused by a mutation of the RASA1 gene located on chromosome 5q13.3 that is responsible for encoding the p120-RasGAP protein. This protein is crucial for normal development of the vasculature.² Although the exact roles of the RASA1 gene and the p120-RasGAP protein are not entirely understood, it is believed that CM-AVMs are caused by a loss or partial loss of function of the gene. One critical function of the RASA1 gene is the conversion of active GTP-bound Ras into its inactive GDP-bound form. A loss of RASA1 function inhibits this conversion and leads to a disruption of the

normal development of the vasculature system. Mutations in the *RASA1* gene have been associated with CM-AVM disorders as well as basal cell carcinoma, suggesting that in CM-AVM mutations there is at least a partial function of the p120-RasGAP protein. This suggests a heterozygous loss of *RASA1* activity with some residual activity in CM-AVM disorder that does not allow tumors to develop, as opposed to homozygous loss in basal cell carcinoma.¹

Typically patients with CM-AVM disorder related to a *RASA1* mutation demonstrate cutaneous findings in the form of capillary malformations—“port-wine stains”—that are low-flow vascular malformations manifesting on the skin as a flat, oval/round, red/pink lesion.³ These patients additionally present with multiple AV malformations (AVM), which are fast-flow lesions that can arise in any area of the body including the skin, bone, brain, or other internal organs.² Cutaneous capillary malformations and AVMs—both considered a hallmark of *RASA 1* mutations—were not present in our patient, but she demonstrated multiple AVF, fast-flow lesion resulting from an abnormal pathway between an artery and a vein, often leading to devastating sequelae such as high-output cardiac failure.⁴ Our patient additionally had multiple pial fistulae, which are extremely rare intracranial vascular malformations with multiple arterial connections to a single venous channel leading to very high pressure and ultimately to poor outcome. Less than 120 cases of pial fistula have been described, mostly in neonates presenting with congestive heart failure.⁵

Our patient suffered an extremely aggressive disease characterized by continuous recurrences and enlargement of treated lesions and relentless, rapid appearance of multiple, new AV communications. Different clinical phenotypes have been reported with *RASA 1* mutations, and we speculate that this newly identified mutation could be related to a purely intracranial phenotype that has not previously been described in the literature.

Conclusion

We report a patient with a new *RASA1* mutation and a new clinical phenotype involving a combination of intracranial AVF and pial fistulae in the absence of AVMs or cutaneous lesions, which are considered the hallmark of this disorder. Because the phenotype appears to be variable, this mutation may be more common than previously estimated.

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FIGURE 1.

Multiple enlarged vessels shown on the initial magnetic resonance image including a large developmental venous anomaly, which is draining the left frontal and parietal lobe. (Inset) Initial computed tomography scan shows skull erosion from the enlarged middle meningeal artery on the left.

FIGURE 2.

Multiple lateral views of the middle meningeal artery with the anterior and posterior branches. (A) Hypertrophy of the middle meningeal artery with venous dilatation (arrow) and multiple fistulae draining into a persistent falcine sinus. (B) Postprocedural complete embolization of the middle meningeal artery with resolution of the fistula connecting this artery to the superior sagittal sinus. (C) Recanalization of the previously embolized middle meningeal artery.