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Large saccular intracranial aneurysm in a child with *RASA1*-associated capillary malformation–arteriovenous malformation syndrome: illustrative case

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BACKGROUND Large cerebral aneurysms are much less common in children than in adults. Thus, when present, these lesions require careful surgical evaluation and comprehensive genetic testing. *RASA1*-associated capillary malformation–arteriovenous malformation (*RASA1*-CM-AVM) syndrome is a rare disorder of angiogenic remodeling known to cause port-wine stains and arteriovenous fistulas but not previously associated with pediatric aneurysms.

OBSERVATIONS The authors report the case of a previously healthy 6-year-old boy who presented with seizure-like activity. Imaging demonstrated a lesion in the right ambient cistern with compression of the temporal lobe. Imaging characteristics were suggestive of a thrombosed aneurysm versus an epidermoid cyst. The patient underwent craniotomy, revealing a large saccular aneurysm, and clip ligation and excision were performed. Postoperative genetic analysis revealed a *RASA1*-CM-AVM syndrome.

LESSONS This is a rare case of a *RASA1*-associated pediatric cerebral aneurysm in the neurosurgical literature. This unique case highlights the need for maintaining a broad differential diagnosis as well as the utility of genetic testing for detecting underlying genetic syndromes in young children presenting with cerebral aneurysms.

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KEYWORDS pediatric; aneurysm; *RASA1*; clip ligation

Cerebral aneurysms are much less common in children than in adults; aneurysms in the first two decades of life account for 1%–4% of all intracranial aneurysms.[1–6] Although the diagnosis and management may be similar in adults and children, the etiology of cerebral aneurysms in children may require genetic investigation because predisposing conditions can be present, and if so, appropriate management should be pursued.[7] In this report, we present the case of a child with a symptomatic, thrombosed, large saccular aneurysm who was found to have *RASA1*-associated capillary malformation–arteriovenous malformation (*RASA1*-CM-AVM) syndrome. This is a rare disease (~1:100,000 prevalence) with only a few cases reported in the literature.[8] The present case highlights the need for physicians to approach aneurysms in children with a high index of suspicion for an underlying genetic predisposition.

Illustrative Case

History, Examination, and Imaging

A previously healthy 6-year-old boy presented to his pediatrician for worsening headaches, photophobia, and right eye pain. The child was born full term with normal cognitive and neurological development. He had incurred a head laceration from a fall from a scooter 2 months before his presentation. His clinical symptoms included conjugate eye

ABBREVIATIONS AVM = arteriovenous malformation; CM-AVM = capillary malformation–arteriovenous malformation; CTA = computed tomography angiography; MRA = magnetic resonance angiography; MRI = magnetic resonance imaging; PCA = posterior cerebral artery; *RASA1*-CM-AVM = *RASA1*-associated capillary malformation–arteriovenous malformation.

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rolling to the right upper quadrant, which was concerning for focal seizures. Additionally, the patient reported increased headaches in the weeks before his presentation, which continued to worsen. Magnetic resonance imaging (MRI) with contrast demonstrated a 15-mm mass lesion located in the ambient cistern with mass effect on the medial aspect of the right temporal lobe. The lesion was in close proximity to the right posterior cerebral artery (PCA) and exhibited hyperintensity on T1- and T2-weighted imaging (Fig. 1A). The patient was started on levetiracetam for seizure prophylaxis and treatment. Comprehensive neurological examination did not reveal any deficits. Skin examination did reveal widespread 1- to 2-cm, pink blanching lesions consistent with capillary malformations. No other soft tissue or skeletal lesions had been previously diagnosed.

Further workup included computed tomography angiography (CTA), repeat MRI, and magnetic resonance angiography (MRA). There was no filling of the lesion apparent on CTA. MRA with three-dimensional reconstructions demonstrated the lesion adjacent to the right PCA, with no definitive clear origin from the PCA (Fig. 1B). Diffusion-weighted imaging demonstrated diffusion restriction throughout the mass lesion, suggesting the possibility of an epidermoid cyst (Fig. 1C). Filtered-phase, susceptibility-weighted imaging demonstrated a thin rim of calcium and intralesional foci of hemosiderin and calcium (Fig. 1D). A 21-channel electroencephalogram revealed results normal for the patient's age and without any observed epileptiform events.

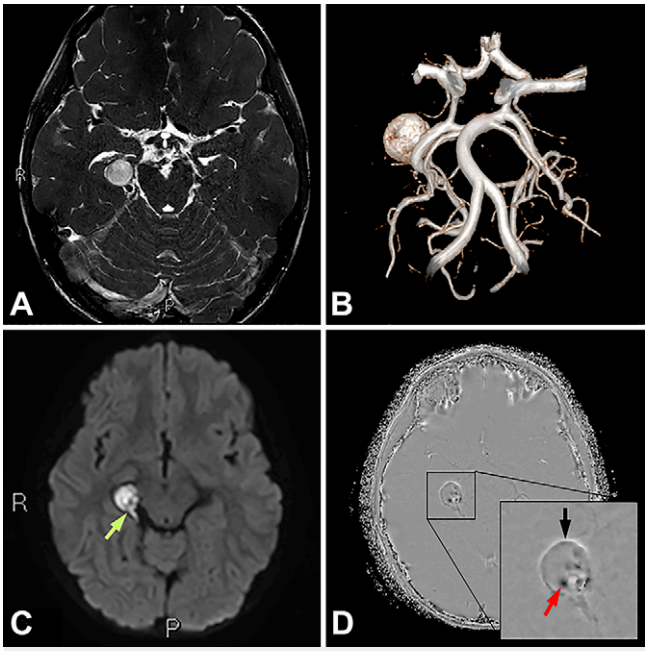

FIG. 1. Preoperative T2-weighted magnetic resonance imaging (**A**) showing a hyperintense 14 × 14 × 15–mm circular lesion within the right ambient cistern. Preoperative three-dimensional magnetic resonance angiography (**B**) demonstrating the lesion adjacent to the right posterior cerebral artery (PCA), suggestive of a cerebral aneurysm. Axial diffusion-weighted image (**C**) demonstrates diffusion restriction with possible connection to the adjacent PCA (*green arrow*). Axial susceptibility-weighted, filtered-phase image (**D**) showing a hyperintense rim of calcification surrounding the lesion (*black arrow*). Dark foci of hemosiderin blood products (*red arrow*) and adjacent bright foci calcium are visible within the lesion.

High-resolution CTA and MRI/MRA did not demonstrate a clear vascular origin; thus, vascular pathology was lower on the differential diagnosis. The comprehensive differential included epidermoid cyst, cerebral cavernous hemangioma, and less likely, thrombosed PCA aneurysm. Digital subtraction angiography was considered but ultimately not performed. A multidisciplinary conference recommended surgical treatment of the lesion and decompression of the medial aspect of the temporal lobe. Conservative and surgical options were discussed with the patient's family, and they chose to proceed with surgical excision of the lesion.

Surgical Treatment

The patient was taken for a right temporal craniotomy with a transcortical approach to the medial temporal lobe. The entry point was made at the middle temporal gyrus, anterior and inferior to the vein of Labbé. Intraoperative navigation with Brainlab Cranial Navigation Brainlab, Munich, Germany was used to assist identifying the location of the cortisectomy. Access to the ambient cistern was gained through the choroidal fissure. Inspection of the lesion revealed that it was white and glossy appearing with a mural, muscular component suggestive of a vascular lesion (Fig. 2). Several areas of the wall demonstrated flecks of fat and calcium deposition. The diagnosis of a vascular lesion, likely an aneurysm, was made intraoperatively. Dense arachnoid adhesions were encountered at the interface between the midbrain and lesion in the ambient cistern, which were sharply dissected until the parent artery, the PCA, was identified. Micro-Doppler was used to confirm biphasic insonation of the proximal and distal PCA in relation to the neck of the aneurysm. Insonation of the aneurysm with the Doppler only revealed flow in the neck, adjacent to the parent vessel. Intraoperative indocyanine green angiography was used to confirm the local angiographic anatomy and flow in the neck of the aneurysm. Two short, curved aneurysm clips were applied to the neck of the aneurysm, and postligation indocyanine green angiography was performed to confirm complete occlusion of the aneurysm. Next, the surgical team performed aneurysmorrhaphy of the dome, which was sent for histopathological evaluation. Hemosiderin and a thrombus were present in the dome of the aneurysm.

The patient had an uncomplicated recovery. He was discharged home on postoperative day 3 with no neurological deficits. He experienced no headaches, seizures, nystagmus, or other neurological deficits in the 2 months following his surgery. Surveillance MRA performed 1 month after surgery demonstrated normal cerebral

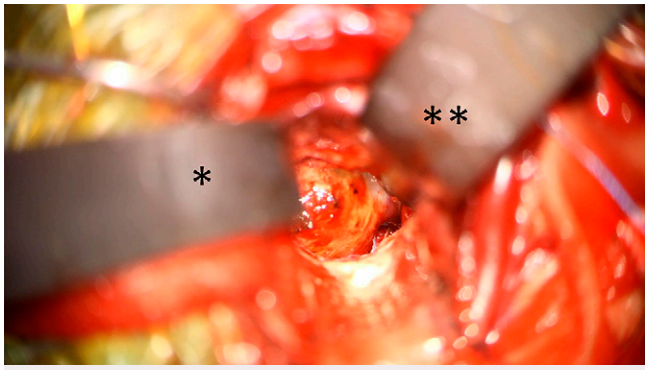

FIG. 2. Intraoperative view of the aneurysm showing anterior (*asterisk*) and posterior (*double asterisks*) retractor placement.

angioarchitecture without evidence of aneurysm recurrence (Fig. 3). The patient was scheduled for 1-year follow-up imaging with digital subtraction angiography.

Pathologic Evaluation

A hematoxylin-and-eosin–stained representative section of the lesion wall with luminal contents (Fig. 4A) demonstrated a well-defined eosinophilic semicircular portion of the aneurysm wall with bright red, adherent luminal contents (consistent with a thrombus). The elastic stain (Fig. 4B) highlighted a thin, wavy gray line on the inner surface of the cyst wall, corresponding to the internal elastic lamina. This structure is peculiar to the arteries and is not present in veins and capillaries. The smooth muscle actin stain (Fig. 4C) depicted smooth muscle cells, which predominate in the inner portion of the arterial media. A trichrome stain (Fig. 4D) demonstrated a diffuse blue staining of the arterial media, indicating extensive fibrosis. These histological features, in concert with the clinical and operative findings, were consistent with a saccular aneurysm.

Genetic Testing

Genetic evaluation of the patient was performed to determine a possible syndromic etiology for the aneurysm. As noted above, the patient had widespread 1- to 2-cm, pink, blanching lesions consistent with capillary malformations. He also had a family history of hernia repair and similar skin lesions in multiple maternal family members. His mother and brother had cutaneous capillary malformations, telangiectasias, hypermobile joints, and hyperextensible skin. These findings were concerning for capillary malformation–arteriovenous malformation (CM-AVM) syndrome, hereditary hemorrhagic telangiectasia (Osler-Weber-Rendu disease), and connective tissue disorders such as vascular Ehlers-Danlos syndrome. Genetic testing using a vascular malformation/stroke next-generation-sequencing gene panel was performed on a buccal swab from the patient, with comparator buccal swab samples provided by both parents. This identified a maternally inherited heterozygous, likely pathogenic variant in RASA1, confirming a diagnosis of *RASA1*-CM-AVM syndrome.

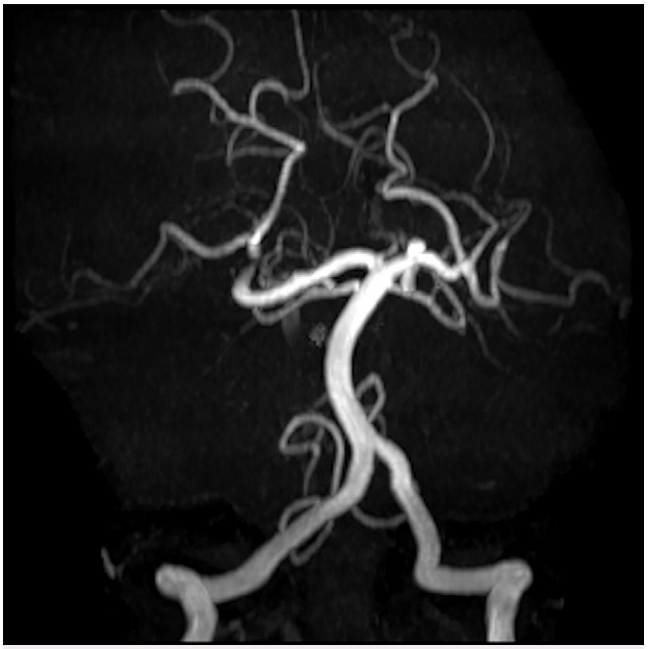

FIG. 3. Magnetic resonance angiography 1 month after surgery demonstrating no evidence of residual or recurrent aneurysm, with patent vasculature and no signs of complication.

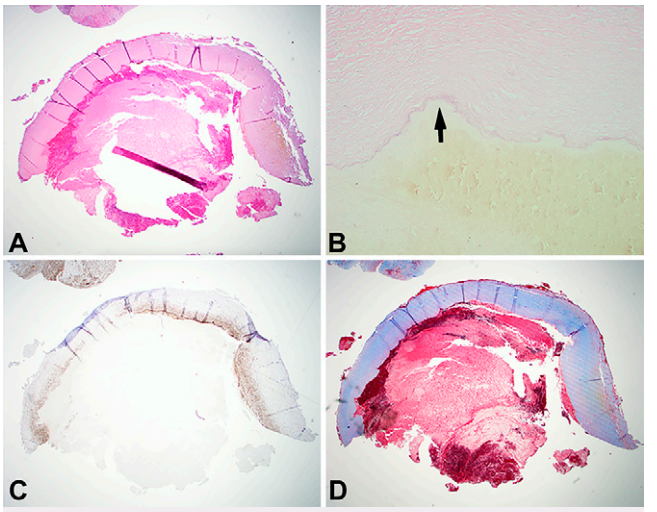

FIG. 4. A: Hematoxylin-and-eosin stain of the arterial wall and luminal thrombus (original magnification ×20). **B:** Elastic stain (arterial wall above, lumen below), with the *arrow* pointing to the internal elastic lamina (original magnification ×200). **C:** Smooth muscle actin stain demonstrating smooth muscle cells in the arterial media (original magnification ×20). **D:** Trichrome stain shows fibrosis of the arterial media (original magnification ×20).

Patient Informed Consent

The necessary patient informed consent was obtained in this study.

Discussion

Observations

The rarity of cerebral aneurysms presenting in children demands that a comprehensive workup be completed to determine their cause. Etiologies of pediatric cerebral aneurysms include trauma, infection, connective tissue diseases, moyamoya disease, sickle cell disease, arteriovenous malformation (AVM), and other genetic conditions.[9] Rupture of the aneurysm can be devastating for pediatric patients, with one study indicating 27% mortality at 1 month and 10%–19% mortality 20 years after diagnosis, mainly due to rebleeding or a de novo aneurysm.[5]

In our patient, the cause of a large, saccular, thrombosed aneurysm was presumed to be *RASA1*-CM-AVM syndrome. *RASA1*-CM-AVM is an autosomal-dominant inherited disorder first described in 2003 by Eerola et al.[10] The RASA1 protein is a RasGTPase that normally reverts active GTP-bound Ras into inactive GDP-bound Ras; pathologic splice variants in this protein are thought to cause premature termination codons within the protein–protein interaction domains of RASA1 that result in inhibition of the conversion of active GTP-bound Ras to inactive GDP-bound Ras.[8] This has been hypothesized to cause abnormal angiogenic remodeling of the primary capillary plexus.[11] As of 2018, 187 different *RASA1* mutations have been identified, with 81% classified as pathogenic.[12] Furthermore, a recent study has proposed that CM-AVM disease development may only occur with a somatic "second-hit" inactivating mutation in a person who already has a germline inactivating the heterozygous *RASA1* mutation.[13]

The classic CM-AVM phenotypic features include small (1–2 cm) pink-red cutaneous capillary malformations (port-wine stains) mostly on the face and limbs, as well as AVMs and fistulas in the skin, muscle, bone, brain, and spine. These malformations can cause a variety of pathologies including congestive heart failure, epilepsy, and aneurysms.[14,15] Previous cases of *RASA1*-CM-AVM presenting in various body regions are summarized in Table 1; these include one previously reported case of an *RASA1*-CM-AVM syndrome–related basilar artery aneurysm.[16] Boccara et al.[17] reported on 68 patients with CM-AVM syndrome and discovered two cerebral aneurysms on central nervous system screening. *RASA1*-CM-AVM syndrome has variable expressivity with wide phenotypic variability within families; this could explain why our patient was the only known member of his family to have CM-AVM presenting with a cerebral aneurysm despite the autosomal-dominant inheritance of this disease. Penetrance of the RASA1 mutation has been reported to be between 90% and 98.5%.[10,18]

The long-term outcomes of children with treated cerebral aneurysms are favorable overall. Recurrence after surgical or endovascular treatment is low, and long-term imaging surveillance helps to identify any recurrences early before they rupture.[5] However, *RASA1*-CM-AVM–related pediatric cerebral aneurysms are rare; thus, recurrence rates and long-term outcomes related to this specific mutation remain unknown. Therefore, a high level of vigilance will be maintained in following this child serially.

In our case, surgical treatment offered definitive diagnosis and cure of the lesion. The importance of having a broad differential diagnosis and augmenting surgical strategy to maximize surgical success and patient safety is key and highlighted in this case.

Lessons

We present the case of a large, saccular aneurysm in a 6-year-old child found to have *RASA1*-CM-AVM syndrome. His aneurysm was successfully clip ligated, and the patient had an uncomplicated postoperative course. The present study underscores the importance of broad differential diagnoses and surgical decision making. For an atypical lesion with any concern for vascular pathology, referral for digital subtraction angiography is indicated. Genetic testing in children who present with aneurysmal malformations as well as their family members is necessary to inform the diagnosis and the potential for family screening. Because of the scarcity of reported cases of *RASA1*-CM-AVM syndrome, more data need to be collected to construct a more complete understanding of this disease process.

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Dr. Ravindra is a military service member. This work was prepared as part of his official duties. Title 17, U.S.C., §105 provides that copyright protection under this title is not available for any work of the US Government. Title 17, U.S.C., §101 defines a US Government work as a work prepared by a military service member or employee of the US Government as part of that person's official duties.

TABLE 1. Literature review of *RASA1*-CM-AVM cases

Authors & Year	No. of Patients	Location(s) of AVM	Clinical Features	Age Range
Eerola et al., 2003[10]	17 affected families, 105 healthy controls	Cutaneous, soft tissue, brain, skeletal, carotid-jugular	Port-wine stain, PWS, cardiac overload	NR
Boon et al., 2005[11]	39	Cutaneous face & foot, intraosseous, brain, carotid-jugular	Port-wine stain, hemiparesis, epilepsy, congestive heart failure, PWS	NR
Thiex et al., 2009[15]	5	Spine	Port-wine stain, headaches, lower-extremity sensorimotor deficits, neurogenic bladder	6–36 yrs
Revencu et al., 2013[18]	261	Cutaneous, brain, face, extremity, spine	Port-wine stain, SWS, mental retardation, epilepsy, basal cell carcinoma, atrial septal defect	NR
Wooderchak-Donahue et al., 2018[8]	281	Brain, extremities, colon, face	Port-wine stain, epistaxis, learning disability, macrocephaly, seizures, tetralogy of Fallot	1 wk–70 yrs
Coccia et al., 2023[19]	4	Cutaneous, vascular	Polyhydramnios, nonimmune hydrops fetalis, chylothorax, increased fetal nuchal thickness	Prenatal
Guimaraes et al. 2022[16]	1	Cerebral	Basilar artery aneurysm; diagnosis preceded cutaneous findings of capillary malformations	Prenatal

NR = not reported; PWS = Parkes-Weber syndrome; SWS = Sturge-Weber syndrome.

References

1. Hetts SW, Narvid J, Sanai N, et al. Intracranial aneurysms in childhood: 27-year single-institution experience. *AJNR Am J Neuroradiol.* 2009;30(7):1315–1324.
2. Kakarla UK, Beres EJ, Ponce FA, et al. Microsurgical treatment of pediatric intracranial aneurysms: long-term angiographic and clinical outcomes. *Neurosurgery.* 2010;67(2):237–250.
3. Koroknay-Pál P, Lehto H, Niemelä M, Kivisaari R, Hernesniemi J. Long-term outcome of 114 children with cerebral aneurysms. *J Neurosurg Pediatr.* 2012;9(6):636–645.
4. Sanai N, Auguste KI, Lawton MT. Microsurgical management of pediatric intracranial aneurysms. *Childs Nerv Syst.* 2010;26(10): 1319–1327.
5. Amelot A, Saliou G, Benichi S, et al. Long-term outcomes of cerebral aneurysms in children. *Pediatrics.* 2019;143(6):e20183036.
6. Nagamitsu S, Kaneko N, Nagatsuna T, et al. Idiopathic dissecting cerebral aneurysm of the distal anterior cerebral artery in an infant successfully treated with aneurysmectomy: illustrative case. *J Neurosurg Case Lessons.* 2021;1(9):CASE20142.
7. Ravindra VM, Karsy M, Schmidt RH, Taussky P, Park MS, Bollo RJ. Rapid de novo aneurysm formation after clipping of a ruptured middle cerebral artery aneurysm in an infant with an MYH11 mutation. *J Neurosurg Pediatr.* 2016;18(4):463–470.
8. Wooderchak-Donahue WL, Johnson P, McDonald J, et al. Expanding the clinical and molecular findings in RASA1 capillary malformation-arteriovenous malformation. *Eur J Hum Genet.* 2018;26(10): 1521–1536.
9. Levy ML, Levy DM, Manna B. *Pediatric Cerebral Aneurysm.* StatPearls; 2023.
10. Eerola I, Boon LM, Mulliken JB, et al. Capillary malformation-arteriovenous malformation, a new clinical and genetic disorder caused by RASA1 mutations. *Am J Hum Genet.* 2003;73(6):1240–1249.
11. Boon LM, Mulliken JB, Vikkula M. RASA1: variable phenotype with capillary and arteriovenous malformations. *Curr Opin Genet Dev.* 2005;15(3):265–269.
12. Bayrak-Toydemir P, Wooderchak-Donahue W. RASA1-related disorders. Published February 2018. Accessed June 30, 2023. https://arup.utah.edu/database/RASA1/RASA1_welcome.php.
13. Lapinski PE, Doosti A, Salato V, North P, Burrows PE, King PD. Somatic second hit mutation of RASA1 in vascular endothelial cells in capillary malformation-arteriovenous malformation. *Eur J Med Genet.* 2018;61(1):11–16.
14. Bayrak-Toydemir P, Stevenson DA. Capillary malformation–arteriovenous malformation syndrome. Adam MP, Mirzaa GM, Pagon RA, et al, eds. *GeneReviews®* [Internet]. University of Washington; 1993–2023. https://www.ncbi.nlm.nih.gov/books/NBK52764/
15. Thiex R, Mulliken JB, Revencu N, et al. A novel association between RASA1 mutations and spinal arteriovenous anomalies. *AJNR Am J Neuroradiol.* 2010;31(4):775–779.
16. Guimaraes MJ, Gomes J, Lopes G, Caldas R, Brito C. Capillary malformation-arteriovenous malformation syndrome associated with basilar artery aneurysm. *Pediatr Dermatol.* 2022;39(4):662–663.
17. Boccara O, Mazereeuw J, Martin L, et al. Central nervous system screening in capillary malformation-arteriovenous malformation syndrome: an observational study. *J Am Acad Dermatol.* 2022; 87(4):914–916.
18. Revencu N, Boon LM, Mendola A, et al. RASA1 mutations and associated phenotypes in 68 families with capillary malformation-arteriovenous malformation. *Hum Mutat.* 2013;34(12):1632–1641.
19. Coccia E, Valeri L, Zuntini R, et al. Prenatal clinical findings in RASA1-related capillary malformation-arteriovenous malformation syndrome. *Genes (Basel).* 2023;14(3):549.

Disclaimers

The views expressed in this article are those of the author and do not necessarily reflect the official policy or position of the Department of the Navy, Department of Defense, nor the US Government.

Disclosures

Dr. Willis reported personal fees from Rady Children's Institute of Genomic Medicine outside the submitted work.

Author Contributions

Conception and design: Ravindra. Acquisition of data: Grice, Willis. Analysis and interpretation of data: Weinberger, Grice, Willis. Drafting of the article: Ravindra, Weinberger, Ikeda, Belverud, Grice. Critically revising the article: Ravindra, Weinberger, Ikeda, Belverud, Grice, Willis. Reviewed submitted version of the manuscript: all authors. Study supervision: Ravindra. Imaging selection and review: Cho.

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