De novo arteriovenous malformation in a patient with hereditary hemorrhagic telangiectasia

Yusuke Shimoda, MD,¹ Toshiya Osanai, MD, PhD,¹ Naoki Nakayama, MD, PhD,¹
Satoshi Ushikoshi, MD, PhD,² Masaaki Hokari, MD, PhD,¹ Hideo Shichinohe, MD, PhD,¹
Takeo Abumiya, MD, PhD,¹ Ken Kazumata, MD, PhD,¹ and Kiyohiro Houkin, MD, PhD¹

¹Department of Neurosurgery, Hokkaido University Graduate School of Medicine; and ²Department of Neurosurgery, Hokkaido Medical Center, Sapporo, Hokkaido, Japan

Hereditary hemorrhagic telangiectasia (HHT) is an autosomal dominant systemic disorder characterized by the enlargement of capillaries, recurrent nosebleeds, and multiple arteriovenous malformations (AVMs). Although cerebral AVMs are traditionally considered to be congenital lesions, some reports have described de novo AVMs, which suggests that the authors believed them to be dynamic conditions. In this article, the authors describe the case of a 5-year-old boy with HHT in whom a de novo cerebral AVM was detected after a negative MRI result at 5 months. To the authors' knowledge, this is the first report of a de novo AVM in a patient with HHT. In patients with a family history of HHT, de novo AVMs are possible, even when no lesions are detected at the first screening. Therefore, regular screenings need to be performed, and the family should be informed that AVMs could still develop despite normal MRI results.

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KEY WORDS hereditary hemorrhagic telangiectasia; de novo arteriovenous malformation; Rendu-Osler-Weber syndrome; vascular disorders

HEREDITARY hemorrhagic telangiectasia (HHT), known as Rendu-Osler-Weber syndrome, is an autosomal dominant vascular dysplasia. It is characterized by the enlargement of capillary vessels, repeated nosebleeds, and multisystemic arteriovenous malformations (AVMs) of the lung, liver, brain, and spinal cord. The incidence of HHT is approximately 1 per 100,000 people, of whom 3.7%–11% develop cerebral AVMs.^{5,20} However, central nervous system complications occur in 48% of all patients with HHT because of paradoxical, air, or septic embolism and in 22%–28% because of cerebral AVMs.^{5,7,34} Cerebral AVMs either enlarge or regress during follow-up, and they occasionally recur after complete resection or radiation therapy.²⁹

The pathogenesis of cerebral AVMs is not fully understood. They are believed to develop due to trauma, infection, radiation therapy, or congenital maldevelopment during Weeks 4–8 of embryonic development; thus, the traditional view has been that de novo AVMs do not exist. However, recent advancements in diagnostic techniques, such as MRI, have led to some reports of de novo

AVMs.^{4,5,33} However, MRI has also failed to detect AVMs on initial scans because of vasospasms or compressions caused by the mass effect of a hematoma or infarction.

Here, we report the case of a 5-year-old child with an AVM that was detected after a headache despite normal MRI results in his infancy. This is a rare case of de novo AVM without an accompanying mass effect. To the best of our knowledge, this is the first report of de novo AVM formation in a patient with HHT.

Case Report

History and Examination

A 5-year-old boy presented with no significant medical history, and a diagnosis of AVM was made. His mother and older brother both had HHT; his mother had undergone surgery for the resection of a cerebral AVM,³⁵ and his brother had suffered from tetraplegia caused by an AVM of the cervical spinal cord.³¹ Based on his family history, he had also undergone screening MRI at 5 months of age, which revealed no lesions of the brain or spinal cord

ABBREVIATIONS AVM = arteriovenous malformation; DSA = digital subtraction angiography; HHT = hereditary hemorrhagic telangiectasia; VEGF = vascular endothelial growth factor.

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FIG. 1. MR images of the patient at 5 months and 5 years of age. **A:** Axial T2-weighted MR images at 5 months of age showing no structural vascular abnormality. **B:** MR image and angiogram at 5 years of age revealing abnormal vascular structures in the right parietal lobe. **C:** Anteroposterior (*upper*) and lateral (*lower*) internal carotid artery injection DSA image demonstrating an AVM recorded as Spetzler-Martin Grade 3 (size 2, eloquent 1, drainer 0).

(Fig. 1A). He had no medical problems except recurrent nosebleeds. At 5 years of age, he suffered from a transient thunderclap headache. Repeat MRI at this presentation revealed an abnormal signal void in the right parietal lobe (Fig. 1B), and cerebral digital subtraction angiography (DSA) revealed a nidus with the predominant arterial supply from the right middle cerebral artery (Fig. 1C). A diagnosis of HHT was made on the basis of family history, recurrent nosebleeds, and evidence of a cerebral AVM; no genetic diagnosis was made (Table 1).

Operation and Postoperative Course

Surgery was performed to eliminate the future risk of hemorrhage. The lesion was resected after copolymer (Onyx) embolization of the 2 arterial feeders (Fig. 2A and B). Subsequent postoperative imaging showed edema around the cavity (Fig. 3). The patient's initial left-sided hemiparesis was successfully managed by rehabilitation; he made a full recovery and was discharged with no neurological deficits. Follow-up DSA after 1 month also showed no residual lesion or recurrence (Fig. 2C).

TABLE 1. Diagnostic criteria for HHT*

Nosebleeds (spontaneous & recurrent)
Mucocutaneous telangiectases (multiple & characteristic sites [i.e., lips, oral cavity, & fingers])
AVM (pulmonary, cerebral, hepatic, spinal, gastrointestinal, &/or pancreatic)
Family history of a first-degree relative in whom HHT has been diagnosed

* A definitive diagnosis is made when 3 or more criteria are met, and possible or suspected diagnosis is made when 2 findings are present.

The diagnosis of AVM was confirmed by pathological examination. H & E staining showed various sizes of vascular structures, including thrombosed vessels. With elastica-Masson and elastica-van Gieson staining, the internal elastic lamina was seen to be poorly formed, and immunohistochemistry showed that vascular endothelial growth factor (VEGF) was localized to the perivascularature. The pathological findings were therefore typical of AVM (Fig. 4).

Discussion

HHT is a systemic genetic disorder, and 3.7%–11% of people affected develop cerebral AVMs. Cerebral AVM is believed to be a dynamic rather than a static condition. Two genes have been shown to be responsible for the development of vascular malformations: the endoglin gene (*ENG*), which is associated with a severe type of HHT (HHT1),²¹ and the activin receptor-like kinase Type 1 (*ALK-1*) gene, which is associated with a less severe type (HHT2).¹² Both genes block the formation of vascular intima, which results in pathological vascular formations.^{12,21} *ENG*, a transforming growth factor β -binding protein, was considered responsible for the dysfunction in tissue repair, angiogenesis, and preservation of vascular structures.

The incidence of cerebral AVMs in children with HHT is unknown. However, MRI is probably an adequate tool for screening. To date, the estimated frequencies of cerebral AVMs have been based on case reports and small series.

In 2006, Giordano et al.⁸ reported that the incidence of occult AVM was 12% in the first-ever cohort of children

FIG. 2. **A:** Preembolization angiograms, anteroposterior (*upper*) and lateral (*lower*) right internal carotid artery views. **B:** Postembolization radiographs of the skull showing Onyx cast, as well as postembolization angiograms, anteroposterior (*upper*) and lateral (*lower*) right internal carotid artery views. **C:** Postoperative DSA images showing gross-total removal of the nidus, anteroposterior (*upper*) and lateral (*lower*) right internal carotid artery views.

in whom it was diagnosed genetically and for whom there was a familial history of HHT. In a sample of 184 consecutive patients with HHT, Fulbright et al.⁷ found 42 cases of cerebral AVM, which suggests a prevalence rate of 23%. However, they included 56 (30%) patients in whom noncontrast MRI was performed, which they accepted as a limitation because it precluded the detection of subtle lesions that could have underestimated the prevalence. Al-Saleh et al.² reported that among symptomatic children with HHT, 5 (24%) of 21 exhibited cerebral AVM.

A previous report stated that de novo AVMs occurred around VEGF-producing tumors,¹⁰ whereas another report stated that multisystemic nidi in an HHT mouse model were expanded in size postnatally after exposure to VEGF-rich conditions such as ischemia, inflammation, and wound healing.³⁷ Thus, there is a close connection between VEGF and HHT. Furthermore, in HHT-associated cerebral AVMs, characteristic findings include small size, multiple locations, cortical lesions, and single drainages.¹⁸ Thus, we believe that, considering data from this

FIG. 3. Postoperative imaging. **A:** Postoperative CT image. **B:** Postoperative MR images showing total removal of the nidus with surrounding edema (diffusion-weighted image [*left*]; fluid-attenuated inversion recovery image [*center*]; and T2-weighted image [*right*]).

FIG. 4. Pathological findings were typical of cerebral AVM. H & E (A), elastica-Masson (B), elastica-van Gieson (C), and VEGF (D), bar = 50 μ m. Figure is available in color online only.

and previous reports (Table 2),^{1,3,4,6,9–11,14,16,19,22–28,30,32,34,36} it is likely that AVMs are not exclusively congenital in origin. That is, AVMs possess dynamic pathophysiological features with the potential for growth and de novo formation.^{1,3,4,6,9–11,13,14,16,19,22–28,30,32,34,36}

A total of 22 patients (including our patient) with de novo AVMs have been reported (Table 2). The majority of these patients were young, and the diagnosis was usually established during childhood. Of the 22 cases, hemorrhagic lesions such as subarachnoid hemorrhages or subdural hematomas were detected in 8 (36.4%) patients. A retrospective review of the imaging in these cases did not reveal any flow voids or areas of focal edema; therefore, hematoma-induced mass effect, vasospasm, or partial thrombosis concealed the AVM. Other common features included seizure in 5 (22.7%) patients and headache in 4 (18.2%) patients.

The previous reports (Table 2) suggest 2 potential hypotheses for the apparent de novo development in our patient. One hypothesis is that the lesions were too small to detect at the first imaging and that some growth factors made the lesions expand in the intervening period to the index presentation. The other possibility is that abnormal flow dynamics were induced by a nidus or drainer thrombosis, whereas our patient showed no mass effect or vasospasm.

We report here the case of a 5-year-old child with a family history of HHT in whom a cerebral AVM was detected after an episode of thunderclap headache; MRI did not reveal the lesion in his infancy. To our knowledge, this is the first report of de novo AVM in a patient with

TABLE 2. Literature review of de novo cerebral AVM cases

Authors & Year	Sex	Initial Imaging Study			Follow-Up Imaging Study				AVM Location	Interval (yrs)
		Age (yrs)	Modality	Reason	Age (yrs)	Modality	Reason			
Porter & Bull, 1969	M	22	DSA	SAH	24	DSA	SAH		Rt PCA territory	2
Krayenbühl, 1977	M	3	DSA	SAH	12	DSA	SAH		Rt frontal	9
Watanabe et al., 1977	M	7	DSA	CSDH	20	DSA	HA		Lt frontal	13
Peeters, 1982	M	3	DSA	SAH	26	DSA	Seizure		Rt frontal	23
Mendelow et al., 1987	F	NA	DSA	SAH	NA	DSA	SAH		Rt occipital	12
Morioka et al., 1988	M	15	DSA	SAH	23	DSA	Seizure		Lt frontal	8
Isayama et al., 1991	M	18	DSA	ICH	20	DSA	ICH		Lt temporal	2
Schmit et al., 1996	M	2	DSA	Seizure	11	DSA	Follow-up		Lt parietal	9
Nussbaum et al., 1998	M	24	DSA	HA	34	DSA	Recurrent HA		Rt cerebellar	10
Freidman et al., 2000	M	61	DSA	Vertigo	63	DSA	Follow-up		Vermis	2
Harris et al., 2000	M	57	DSA	HA	57	DSA	Follow-up		Rt occipital	6*
Rodríguez-Arias et al., 2000	F	9	DSA	Seizure	11	DSA	Follow-up		Rt parietal	2
Bulsara et al., 2002	F	26	DSA	Infection	32	DSA	HA		Rt temporal	6
Akimoto et al., 2003	F	10	DSA	IVH	27	DSA	IVH		Lt occipital	17
Miyasaka et al., 2003	F	50	DSA	HA	58	DSA	SAH		Rt parietal	8
Gonzalez et al., 2005	F	3	MRI	Seizure	7	MRI	Epilepsy		Rt temporal	4
O'Shaughnessy et al., 2005	F	6	MRI	SCD	6	DSA	Examination		Rt sylvian fissure	Immediately
Mahajan et al., 2010	F	16	MRI	Bell's palsy	30	MRI	Migraine/seizure		Lt frontoparietal	14
Stevens et al., 2009	F	6	MRI	Seizure	9	MRI	Seizure		Lt temporooccipital	3
Alvarez et al., 2012	M	6	MRI	Seizure	8	MRI	Follow-up		Rt temporooccipital	2
Kilbourn et al., 2014	M	11	MRI	Post-VPS	18	DSA	HA		Brainstem	7
Present study	M	5†	MRI	Screening	5	DSA	HA		Rt parietal	5

CSDH = chronic subdural hematoma; HA = headache; ICH = intracerebral hemorrhage; IVH = intraventricular hemorrhage; NA = not available; PCA = posterior cerebral artery; SAH = subarachnoid hemorrhage; SCD = sickle cell disease; VPS ventriculoperitoneal shunt.

* This interval is expressed in weeks.

† This age is expressed in months.

HHT, although Komiyama¹⁵ mentioned the possibility that human cerebral AVMs could form until 2 years of age. AVMs seem to be dynamic conditions; in some cases they enlarge, whereas in others they regress or disappear (see Table 2). Previous reports have emphasized the need for repeated DSA in cases of childhood HHT, even if the first screening MRI results were negative.¹⁷ However, there is currently no consensus on an adequate period of time between the first and second screenings. Considering this case, we recommend that an annual screening MRI be performed. In patients with a family history of HHT, de novo AVMs are possible, even when no lesions are detected at the first screening. Therefore, regular screenings need to be performed, and the family should be informed that AVMs can still develop despite normal MRI results.

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Disclosures

The authors report no conflict of interest concerning the materials or methods used in this study or the findings specified in this paper.

Author Contributions

Conception and design: Shimoda. Acquisition of data: Shimoda. Drafting the article: Shimoda. Critically revising the article: all authors. Approved the final version of the manuscript on behalf of all authors: Shimoda.

Correspondence

Yusuke Shimoda, Department of Neurosurgery, Hokkaido University Graduate School of Medicine, North 15 West 7, Kita-ku, Sapporo Hokkaido 060-8638, Japan. email: shimoda-hok@umin.ac.jp.