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Clinical commentary

Clinical presentation and treatment paradigms of brain arteriovenous malformations in patients with hereditary hemorrhagic telangiectasia

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ABSTRACT

Hereditary hemorrhagic telangiectasia (HHT) is characterized by recurrent spontaneous epistaxis, mucocutaneous telangiectases, and multisystem arteriovenous malformations (AVMs). Brain AVMs typically present at birth and are identified in approximately 10–20% of patients with HHT. A retrospective review was undertaken of all HHT patients with known single or multiple brain AVMs treated at our institution. Thirty-nine patients with brain AVM(s) were diagnosed with HHT. Most patients presented with at least one Curaçao criterion. A total of 78 brain AVMs were identified in 39 patients. Two-thirds of patients had solitary brain AVMs, whereas 33% of patients harbored at least two lesions (range: 2–16). Brain AVMs of the supratentorial cerebral hemispheres comprised 83% of all lesions, whereas infratentorial lesions accounted for only 17%. Of the 55 brain AVMs assigned Spetzler-Martin grading, the majority of patients were Grade 1 (73%), and 23% and 4% were Grades 2 and 3, respectively. Patients were treated with surgery alone (51%), embolization alone (6%), embolization followed by surgery (9%), stereotactic radiosurgery (11%), stereotactic radiosurgery followed by surgery (3%), or observation (20%). Of patients who underwent genetic analysis, 62% possessed mutations in *ENG* (HHT type 1), whereas 38% had mutations in *ACVRL1* (HHT type 2). This robust patient cohort of brain AVMs in 39 patients with HHT advances the collective understanding of this disease's varied presentation, diagnostic workup, genetic underpinnings, and available treatment options.

1. Introduction

The autosomal dominant angiodysplastic disorder hereditary hemorrhagic telangiectasia (HHT) or Osler-Weber-Rendu disease affects the vasculature of numerous organ systems. HHT has an estimated prevalence of 1 in 5000–10,000 individuals and is clinically characterized by recurrent spontaneous epistaxis, mucocutaneous telangiectases, and arteriovenous malformations (AVMs) of the gastrointestinal, hepatic, pulmonary, and central nervous systems (CNS) [1–3]. Hemorrhage, stroke, cerebral abscess, and shunting represent potentially devastating complications of AVMs, particularly those that are large and involve the liver, lungs, or CNS [4]. Causative gene mutations have been demonstrated to modulate the transforming growth factor-beta (TGF-β) superfamily of signaling molecules, leading to altered endothelial cell signaling and dysregulation of embryonic patterning, angiogenesis, blood vessel remodeling, and maturation [4–6]. Collectively, altered development and/or maintenance of organ system vasculature leads to tortuous, leaky, telangiectatic vessels and vascular malformations (i.e., AVMs) lacking an interposed arterial–venous capillary bed. These abnormal vessels have a greater tendency toward spontaneous hemorrhage, especially in younger HHT patients with intracranial vascular malformations [7,8].

The multisystemic vascular dysplasia in HHT derives from several well-characterized genes, mutations in which cause high, but age-related, penetrance and variable expression [9]. These commonly mutated genes encode endoglin (*ENG* gene, 9q34.11; HHT type 1), activin receptor-like kinase type 1 (*ACVRL1* gene, formerly *ALK1*, 12q13.13; HHT type 2), SMAD4 (18q21.2; HHT associated with juvenile polyposis), and very rarely, BMP9 (*GDF2* gene, 10q11.22) proteins. Furthermore, new mutations are regularly reported and the actual number of mutations is much higher than previously thought [5,10]. There is significant evidence to suggest

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Table 1
Summary of characteristics and presentations of HHT patients with brain AVMs.

Pt #	Age (years)	Age at diagnosis (years)	Sex	HHT type	Mutation	Presentation	Diagnostic approach	Hemorrhage	Other HHT manifestations	Family history
1	21	15	M	HHT2	ACVRL1 (exon 10 del)	Family history	MRI, MRA, angiography	N	Epistaxis, MCTs	Y
2	74*	57	M	HHT2	ACVRL1 (c.998G>T)	ICH	MRI, angiography	Y	Epistaxis, MCTs	Y
3	37	31	M	HHT1	ENG (c.1A>T)	NA	MRI, MRA	N	PAVMs (×2)	Y
4	35	29	M	HHT1	ENG (c.1A>T)	Family history, epistaxis	MRI, MRA	N	Epistaxis, MCTs, PAVM	Y
5	0.75*	9 days	M	HHT NFS	NA	NA	MRA, angiography	NA	None	NA
6	48	34	F	HHT NFS	NA	NA	CT	NA	None	NA
7	13	0.5	M	HHT NFS	NA	NA	MRI, MRA	NA	None	NA
8	66	53	M	HHT2	ACVRL1 (IVS4 + 3 A>G)	Brain abscess, PAVM	CTA, MRI	N	Epistaxis, MCTs, PAVMs (×2), numerous HAVMs	Y
9	45	19	F	HHT1	ENG (exon 5, c.587G>A)	Family history	Angiography	Y (R frontal, L frontal, L temporal lobe lesions)	Epistaxis, MCTs, PAVMs (×2)	Y
10	19	0 (birth)	F	HHT1	ENG (NFS)	Family history	MRI	N	Epistaxis, MCTs, PAVM	Y
11	14*	11	F	HHT2	ACVRL1 (p.K487T)	Heart failure, pulmonary arterial hypertension	MRI	N	Epistaxis, MCTs, multiple PAVMs	N
12	69	35	F	HHT1	ENG (exon 6, c.755 T>A)	Epistaxis	MRI, MRA	N	Epistaxis, MCTs, PAVM, numerous HAVMs	Y
13	28	16	F	HHT1	ENG (exon 6, c.808C>T)	Headache	MRI	Y (R parietal lobe lesion)	Epistaxis, MCTs, numerous PAVMs	N
14	26	16	F	HHT1	ENG (c.816 + 2 T>C)	Epistaxis	MRI	N	Epistaxis, MCTs, PAVMs (×7)	Y
15	37	16	F	HHT2	ACVRL1 (c.86delG)	Epistaxis, headache	CTA, angiography	N	Epistaxis, MCTs, PAVM, HAVM	Y
16	53	20	F	HHT NFS	NA	ICH during pregnancy	MRI	Y	Epistaxis, PAVM	N
17	29	10	F	HHT1	ENG (c.525 + 2 A>G)	Epistaxis	CT, MRI, MRA, angiography	N	Epistaxis, MCTs, PAVM	Y
18	53	49	M	HHT2	ACVRL1 (exon 3–7 del)	ICH, epistaxis	CT	Y	Epistaxis, MCTs	Y
19	54	39	M	HHT2	ACVRL1 (c.1120C>T)	Family history, epistaxis	Angiography	N	Epistaxis, MCTs, PAVM, numerous HAVMs	Y
20	62	44	F	HHT1	ENG (c.1640 T>G)	NA	MRI, MRA	N	Epistaxis, MCTs, multiple PAVMs	Y
21	58	41	M	HHT1	ENG (c.525-2A>G)	NA	MRI	N	Epistaxis, MCTs, PAVM	Y
22	22	17	M	HHT2	ACVRL1 (c.998G>T)	Family history	MRI, MRA	N	Epistaxis, MCTs	Y
23	55	51	M	HHT1	ENG (exon 9–10 del)	Family history	MRI	Y (at age 29)	Epistaxis, MCTs	Y
24	27	23	M	HHT2	ACVRL1 (intron 5, c.626–17-7del11ins14)	Family history, headache	MRI, angiography	N	Epistaxis, MCTs, PAVMs (×2)	Y
25	41	37	F	HHT1	ENG (c.1A>G)	Family history, anemia	MRI, angiography	N	Epistaxis, MCTs, PAVM	Y
26	55	35	M	HHT NFS	NA	Brain abscess (R parieto-occipital)	MRI, angiography	N	Epistaxis, multiple PAVMs	NA
27	76	20	F	HHT NFS	NA	Headaches	MRI, angiography	N	Epistaxis	N
28	37	0.5	M	HHT NFS	NA	ICH	CT	Y	Epistaxis, MCTs, PAVMs (×3)	Y
29	40	17	F	HHT1	ENG (C.1085dupA)	Family history	MRI, MRA, CTA	N	Epistaxis, MCTs, PAVM	Y
30	58	57	F	HHT NFS	NA	Epistaxis	MRI	N	Epistaxis, MCTs, numerous HAVMs, pancreatic AVM	N
31	37	NA	M	HHT NFS	NA	Headache	MRI, angiography	N	Epistaxis	N
32	72	NA	M	HHT NFS	NA	Epistaxis	MRI	N	Epistaxis	Y
33	55	NA	M	HHT NFS	NA	Family history	MRI	N	Epistaxis	Y
34	22	NA	M	HHT NFS	NA	NA	MRI	N	Multiple PAVMs	NA
35	44	16	F	HHT1	ENG (exon 5 del)	Epistaxis	MRI	N	Epistaxis, MCTs, multiple PAVMs, gastrointestinal telangiectases (3)	Y

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