BMC Neurology

CASE REPORT

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Hereditary haemorrhagic telangiectasias with recurrent ischemic stroke hinted by manganese deposition in the basal ganglia: a case report and literature review

Qiwen Tang[1], Ping Xia[1], Xingyue Hu[1*] and Yuquan Shao[1*]

Abstract

Background Hereditary hemorrhagic telangiectasia (HHT) is a rare autosomal dominant inherited vascular disorder that can involve multiple organs, thus can be associated with so many clinical departments that proper screening and diagnosis of HHT are needed for providing better management of both patients and their family members.

Case presentation We present a 58-year-old female patient with recurrent paradoxical brain embolism due to HHT. She received aspirin therapy and underwent pulmonary arteriovenous malformation embolization, recovering well and discharged 3 days postoperatively. Though ischemic stroke caused by HHT-induced vascular disorders has been reported, our patient presented with both recurrent paradoxical brain embolisms and radiologic findings of bilateral globus pallidus manganese deposition at the same time, a combination rarely reported. We also review the literature on the clinical features and management of HHT for prompt diagnosis of this genetic disease behind paradoxical embolism.

Conclusions When patients with ischemic stroke, especially recurrent ischemic stroke, have combined arteriovenous malformations (AVMs) in single or multiple organs, or clues for AVMs like manganese deposition in globus pallidus, genetic diseases such as HHT may be the reason for ischemic stroke and shouldn't be missed in the evaluation of embolic sources.

Keywords Ischemic stroke, Hereditary hemorrhagic telangiectasia, Arteriovenous malformations, Manganese deposition, Case report

*Correspondence:
Xingyue Hu
huxingyue2003@zju.edu.cn
Yuquan Shao
yq_shao@zju.edu.cn
[1]Department of Neurology, Sir Run Run Shaw Hospital, School of Medicine, Zhejiang University, Hangzhou, Zhejiang, China

Background

Hereditary hemorrhagic telangiectasia (HHT), also known as Rendu–Osler–Weber syndrome, is a rare autosomal dominant inherited vascular dysplasia, containing arteriovenous malformation(AVM) and telangiectasia of skin, mucous membranes especially nasal, and internal organs like gastrointestinal tract, lung, liver, as well as the brain [1].

Notably, HHT is not as rare a disease among Asians as researchers used to think but is easy to miss [2], as the prevalence of HHT was estimated to be approximately 1 in 1300 to 1 in 10,000 individuals varying in different regions [3–6]. Among HHT patients, approximately 15–50% of them are affected by pulmonary arteriovenous malformation (PAVM), but the proportions differ according to HHT genotype [7–9]. Interestingly, HHT is the most common cause of PAVM with a proportion of approximately 70% [10]. PAVM can cause paradoxical embolism in ischemic stroke. Paradoxical embolism happens when the clot originating in the venous system or right heart chambers passes through an intracardiac shunt like patent foramen ovale (PFO) or extracardiac shunt like PAVM directly into the systemic circulation [11].

Basal ganglia T1 hyperintensity, observed in >23% of HHT patients, is commonly found in the central nervous system. This hyperintensity is typically attributed to intracranial manganese deposition associated with hepatic arteriovenous shunts [12]. Interestingly, iron deficiency as a common symptom of HHT can also collaborate with the increase of manganese absorption and deposition in basal ganglia leading to neuropsychological impairment, or occasionally parkinsonism [12–14]. Additionally, manganese deposition in the basal ganglia can also be associated with various conditions, including long-term total parenteral nutrition therapy, prolonged manganese exposure, protein malnutrition, biliary diseases, renal dysfunction, thyroid disorders, and abnormalities in trace element metabolism (such as calcium, magnesium, zinc, and copper) [15].

This report demonstrates a case of recurrent ischemic stroke due to paradoxical embolism from PAVM, which was considered caused by HHT. The case is attractive because its radiologic finding of basal ganglia T1 hyperintensity, indicative of manganese deposition, which may serve as a potential indicator of undiagnosed HHT and the underlying cause of stroke.

This case is reported according to CARE guidelines.

Case presentation

A 58-year-old woman had sudden right-sided numbness without apparent trigger 3 days before admission, mainly in the right lower limb. She denied stroke risk factors such as smoking, hypertension, hyperlipidemia, diabetes, and atrial fibrillation, but had a history of ischemic stroke two years ago, presenting with right limb numbness and no residual neurological deficits after treatment and secondary stroke prevention. She has had multiple episodes of epistaxis, and iron-deficiency anemia for years.

On examination, sensation to vibration was slightly impaired in the right extremities, while other neurological assessments, including cranial nerves, motor function, and reflexes, showed no significant abnormalities. Besides, multiple small haemangioma-like telangiectatic lesions were observed on the tongue and various parts of the skin, apart from which, no significant abnormalities were noted in other systems. The patient's father, grandfather, siblings, and kids also had a history of epistaxis.

Laboratory investigation showed mild iron-deficiency anemia with a positive fecal occult blood test and slightly elevated D-dimer. Renal function, liver function, C-reactive protein level, and hemoglobin A1c level were all in normal ranges.

MRI of the head revealed a recent infarct in the left fronto-parietal lobe and insula (Fig. 1a and b), and bilateral globus pallidus showed patchy high signal intensity on T1-weighted images, indicating manganese deposition (Fig. 1c). No cerebral arterial abnormality was found by the assessment of magnetic resonance angiography. Aortic and carotid ultrasonography were negative for atherosclerotic plaques. Deep and bilateral iliac veins of both lower limbs were normal via ultrasonography. Chest computed tomography (CT) image demonstrated a mass shadow in the right lower lung field, suggesting a vascular malformation. Also, a bubble contrast study disclosed a right-to-left shunt with transcranial Doppler, which suggested the existence of a right-to-left shunt. Thus, we performed a chest CT with contrast revealing a PAVM in the right lower lung (Fig. 1d), while transthoracic echocardiography showed an atrial septal aneurysm. Subsequently, transesophageal echocardiography was performed and found an atrial septal aneurysm, yet no PFO or thrombus. In addition, a dynamic electrocardiogram (ECG) examination found occasional atrial premature beats and ventricular premature beats. Additionally, hepatic enhanced contrast CT was performed, and it demonstrated portal vein to hepatic vein shunt and obvious dilation of hepatic arteries (Fig. 1e and f). However, the patient denied a history of hepatic encephalopathy and any prior occurrences of asterixis. Also, blood ammonia levels were normal at the time of admission.

This patient received antithrombotic therapy with aspirin, and underwent embolization of PAVM 14 days after

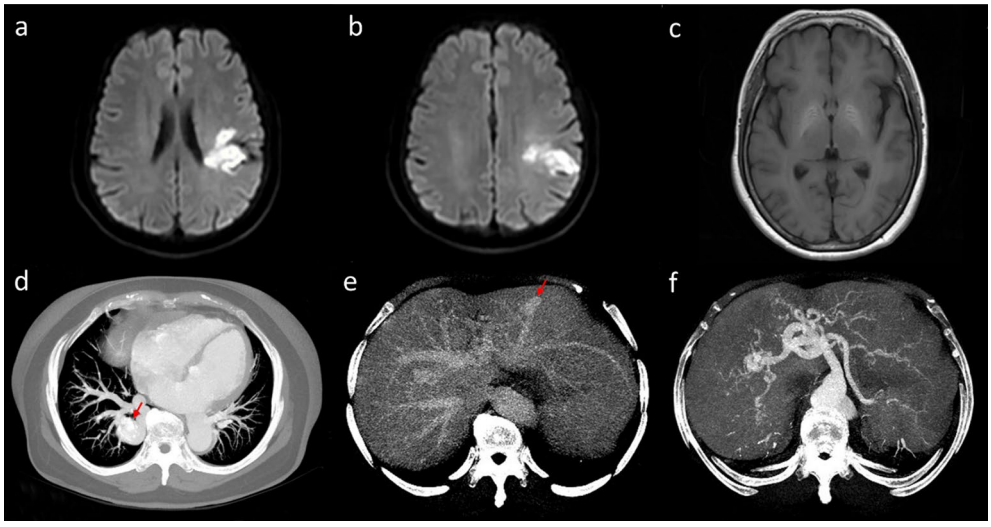

Fig. 1 Brain MRI performed 5 days after symptom onset revealed recent infarctions (**a**, **b**). Basal ganglia hyperintensity on axial T1-weighted MR imaging (**c**). A PAVM in the right lower lung on CT with contrast (arrow) (**d**). Portal vein to hepatic vein shunt (arrow) (**e**) and obvious dilation of hepatic arteries (**f**) on CT with contrast

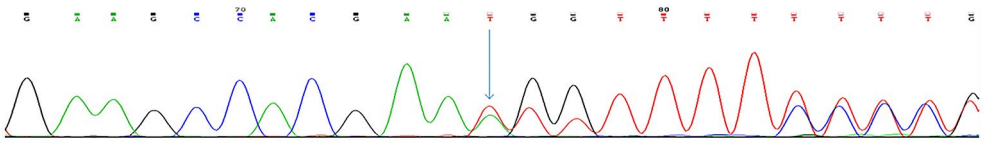

Fig. 2 High-throughput sequencing showed a variant, ENG_ex7 c.861dup (p.Arg288SerfsTer46)

the onset of symptoms. A 14 mm × 10 mm plug and a 10 mm × 30 cm coil were each implanted for embolization. Postoperative pulmonary angiography showed the disappearance of the pulmonary arteriovenous fistula. In addition, iron supplement therapy was prescribed to the patient. She was discharged on the third day after the gradual recovery from the surgery.

High-throughput sequencing tested positive for a variant, ENG_ex7 c.861dup(p.Arg288SerfsTer46), resulting in the premature termination of the protein coding sequence (Fig. 2). Considering that several family members of this patient also had a history of epistaxis, genetic counseling was recommended, but they refused.

Discussion

Our patient had a recurrent ischemic stroke, with a history of epistaxis as well as her family members. She also presented with telangiectasia on the tongue and skin, and gastrointestinal bleeding likely due to telangiectasia as well. Additionally, hepatic AVM and PAVM were identified. These findings matched well with the four consensus diagnostic criteria of HHT, described as epistaxes, telangiectasia, visceral lesions, and a family history of a first-degree relative in Curaçao criteria [16].

According to the ACMG guideline, the variant of our patient was judged to be pathogenic, and it was not included in the ClinVar database. ENG gene encodes a major glycoprotein of the vascular endothelium, endoglin [14], while the mutation detected may cause the malfunction of the protein coded and eventually result in vascular dysplasia. A former study found that PAVM was more frequent in patients with the ENG variant [17]. Thus, paradoxical embolism due to PAVM is one of the reasons that shouldn't be ignored while diagnosing stroke and also embolism in various other organs, especially for those young patients with no vascular risk factors but symptoms may be caused by vascular abnormality suspected to be HHT.

Despite recurrent ischemic stroke due to PAVM, our patient uniquely presented with manganese deposition in bilateral globus pallidus, yet no extrapyramidal symptoms were observed. Considering that the liver is the principal organ responsible for manganese metabolism, we inferred and ultimately did confirm that the patient have underlying hepatic issues. Interestingly, in addition to hepatic AVMs, researchers have suggested that iron deficiency might also contribute to the aggravation of manganese deposition in the basal ganglia [18–20].

Therefore, iron supplementation could theoretically help prevent manganese deposition, and is worth considering. Although manganese deposition can result from other causes, in this case, the simultaneous presence of telangiectasia, AVMs, and epistaxes strongly suggests that manganese deposition is primarily associated with HHT-related hepatic AVMs, as supported by the Curaçao criteria [16]. Notably, manganese deposition is common in HHT patients and was reported in over 23% of a cohort of 312 HHT patients [12]. Also, this study denied the association between increased signal intensity and gross neurologic disturbances, yet it demonstrated that basal ganglia T1 high signal intensity is significantly associated with older age, hepatic AVM, hepatic telangiectasia, hepatic failure, and high cardiac output; but not with sex, the genetic mutation status, or clinical parkinsonism. However, that study didn't discuss the association between globus pallidus hyperintensity and iron-deficiency anemia in HHT patients.

Management of HHT was patient-tailored, and mainly implemented to improve and control the symptoms. Treatment of PAVMs by embolization is recommended as a safe and effective therapy when the afferent artery of the malformation is at least 1 to 3 mm depending on the expertise of the radiologist [21, 22]. Despite our concerted efforts to reach the patient and her family, we were unfortunately unable to obtain postoperative follow-up information. Besides, liver transplantation rather than endovascular interventional therapy was considered a choice of treatment for those who failed medical treatment. Recently, studies on pharmacological treatments such as antifibrinolytic therapy and angiogenesis inhibitors have been used to treat patients and showed promising results. However, larger sample size research was still lacking [23].

Literature review

To our knowledge, Joel Agarwal et al. [24] summarized the information of 8 non-case studies and 15 case studies from MEDLINE and EMBASE about HHT patients with PAVM and neurological complications, including ischemic stroke and transient ischemic attack (TIA). Then we here provided both non-case studies (Table 1) [25–31] and case studies (Table 2) [32–34] related to HHT patients with PAVM-induced ischemic stroke as well as TIA from 2017 to 2023. The non-case studies we showed in Table 1 tended to discuss the correlation between PAVM and stroke in general or PAVM population, rather than in the HHT cohorts. Asian patients were diagnosed with HHT in 37.7% of the PAVM patients in the study of Xu Ma et al. [26], which was less frequent than in Western groups, and mostly female. The study also showed no correlation between the characteristics of PAVM and the severity of TIA or stroke, while Johan Etievant et al. [29] held the opposite opinion. Additionally, patients with HHT-related PAVM had a greater rate of ischemic stroke than the general population [27, 29, 30]. Interestingly, besides the general population, the study by Laura Delagrange et al. has delineated that, contrary to expectations based on the potential for pregnancy-related hemodynamic changes to exacerbate shunting through aberrant vascular beds, severe cerebrovascular complications in women with HHT during pregnancy are notably infrequent [25]. Beyond the AVMs that are typically the focus in HHT patients, our case identifies T1 hyperintensity in the basal ganglia as a potential indicator of HHT, particularly in patients with elevated stroke risks. HHT can lead to various symptoms, thus usually involving a great many clinical departments. Also, older patients may have limited management options, highlighting the significance of full knowledge and prompt diagnosis of this population.

Table 1 Literature review of HHT with PAVM-induced ischemic stroke (non-case studies)

Author. [Ref] Year	Study design	Region	HHT (Female)	PAVM-induced Ischemic Stroke* (Female)	HHT diagnosis	PAVM diagnosis	Gene	Key results
Laura Delagrange et al. [25] 2023	Retrospective	France	*N* = 207 (207)	*N* = 2 (TIA) (2)	Clinical and/or genetic diagnosis	Not mentioned	ENG	- Although severe cerebrovascular complications in pregnant women with HHT are infrequent, they can be mitigated through preconception education on screening protocols and potential pregnancy-associated risks.
Xu Ma et al. [26] 2022	Retrospective	China	*N* = 78 (57)	—	Curaçao criteria	MSCT or CTA	Not mentioned	- Small PAVMs (< 3 mm diameter of feeding artery) should also be treated in patients who develop serious manifestations such as stroke or brain abscess.
Karan K Topiwala et al. [27] 2021	Retrospective	The United States	*N* = 106 (Not mentioned)	—	Not mentioned	Not mentioned	Not mentioned	- Iron deficiency anemia (not only HHT-related) was an independent stroke risk marker in patients with PAVFs for acute ischemic stroke, and the potential mechanisms include enhanced platelet aggregation, impaired oxygen delivery, and high blood viscosity.
Torbjörn Karlsson et al. [28] 2018	Retrospective	Sweden	*N* = 21 (Not mentioned)	—	Curaçao criteria	Not mentioned	ENG, ACVRL1, and SMAD4	- Nearly one in five patients in the HHT population has been diagnosed with stroke or cerebral abscess. - PAVMs are higher in HHT1 (ENG, 60%), whereas hepatic AVMs are more common in HHT2 (ACVRL1, 38%). – 62% of HHT patients were diagnosed with iron deficiency anemia (no difference between HHT1 and HHT2).
Johan Etievant et al. [29] 2018	Retrospective	—	*N* = 170 (92)	*N* = 28 (Not mentioned)	Curaçao criteria	Chest CT	ENG, ALK1, and SMAD4	- The CT characteristics of PAVMs exhibit a significant correlation with the risk of ischemic stroke, particularly with those PAVMs featuring larger feeding arteries.
Waleed Brinjikji et al. [30] 2017	Retrospective	The United States	*N* = 353 (Not mentioned)	*N* = 25 (SBI) (Not mentioned)	Curacao criteria or genetic diagnosis	Chest CT	ENG, ALK1, and SMAD4	- The prevalence of SBI among patients with HHT and PAVMs was elevated in comparison to the general population, particularly in individuals over the age of 60, while the prevalence was less in HHT patients without PAVMs.
Emanuele Boatta et al. [31] 2017	Retrospective	France	*N* = 4 (4)	*N* = 1 (TIA) (1)	Not mentioned	Echocardiogram/bubble test and contrast-enhanced CT	Not mentioned	- Micro Vascular Plugs embolization for PAVMs is technically feasible, straightforward, safe, and effective in early follow-ups. The long-term safety and efficacy of this novel technique require further prospective validation.

HHT hereditary haemorrhagic telangiectasia; PAVM pulmonary arteriovenous malformation; TIA transient ischemic attack; MSCT multi-slice spiral computed tomography; CTA computed tomography angiography; PAVF pulmonary arteriovenous fistula; CT computed tomography; SBI silent brain infarct

* Patients of PAVM-induced ischemic stroke (or other ischemic cerebrovascular diseases) among HHT patients

Table 2 Literature review of HHT with PAVM-induced ischemic stroke (case reports)

Author. [Ref] Year	Age (Female)	Manifestation	PAVM	Infarcted areas	Gene	Treatment	Follow up	Key results
Keishiro Sueda et al. [32] 2020	45	Deficits in the left visual fields of both eyes.	-Chest CT with contrast -In the right upper lobe	A large posterior cerebral artery infarct in the right occipital lobe.	Declined	The anticoagulant was discontinued after 2 months of embolotherapy was performed.	-The visual field deficit was completely resolved at the time of discharge. -Two-year CT of the chest: did not show recanalization or new lesions.	- For patients presenting with hepatic shunt manifestations, including portal hypertension, high-output cardiac failure, intestinal steal syndrome, and jaundice, it is advisable to conduct either doppler ultrasonography or abdominal CT to identify hepatic vascular malformations.
Xu Lu et al. [33] 2020	19	- Progressive paralysis of the right arm, worsening of aphasia, and salivation. - A history of epistaxis.	-CTPA -Two feeding arteries of 7.43 and 4.95-mm diameter in the left lower lobe	Infarcts in the left frontal, temporal, insular, parietal, and right frontal lobes.	Declined	Embolotherapy for PAVM.	Six-month CTPA: no recanalization.	- Symptoms associated with pulmonary dysfunction, such as cyanosis and hypoxemia, in patients with recurrent ischemic stroke may suggest the presence of HHT-related PAVMs.
Rano Abdulla Kyzy et al. [34] 2019	91(F)	-Gradually reducing mobility. -Pallor, wide-spread cutaneous telangiectasia, and recurrent epistaxis.	-CTPA -A large PAVM in the middle lobe of the right lung	Lacunar infarcts (no specific areas mentioned).	Not mentioned	-Embolization for PAVM was considered but risks were felt to outweigh the benefits due to the patient's frailty. -Home oxygen therapy.	Not mentioned.	- The patient presented with microcytic anemia and mild polycythemia.

HHT hereditary haemorrhagic telangiectasia; PAVM pulmonary arteriovenous malformation; CT computed tomography; ESUS embolic stroke of undetermined sources; CNS central nervous system; CTPA computed tomographic pulmonary angiography

Conclusion

This case reminds us that a stroke with bilateral globus pallidus hyperintensity on T1-weighted images can arise from HHT. Some assessments for genetic diseases like HHT are needed when patients with stroke are recognized to have AVM such as PAVM and hepatic AVM, leading to the prevention of complications in patients and better screening of the diseases in family members.

Abbreviations

HHT	Hereditary hemorrhagic telangiectasia
AVM	Arteriovenous malformation
PAVM	Pulmonary arteriovenous malformation
PFO	Patent foramen ovale
CT	Computed tomography
MRI	Magnetic resonance imaging
ECG	Electrocardiogram
TIA	Transient ischaemic attack
MSCT	Multi-slice spiral computed tomography
CTA	Computed tomography angiography
PAVF	Pulmonary arteriovenous fistula
SBI	Silent brain infarct
ESUS	Embolic Stroke of undetermined sources
CNS	Central nervous system
CTPA	Computed tomographic pulmonary angiography

Acknowledgements

None.

Author contributions

QT: acquisition and analysis of the data, and drafting of the manuscript; YS and XH: design of the work and revision of the manuscript; PX: acquisition of written informed consent and revision of the manuscript. YS and XH are co-corresponding authors. All authors reviewed the manuscript.

Funding

No funding was needed to conduct this study.

Data availability

The datasets used and analyzed during the current study are available from the corresponding authors upon reasonable request. The datasets of high throughput sequencing in the study are available in the SRA repository, Accession number: SRR26670635.

Declarations

Ethics approval and consent to participate

Ethics approval was unnecessary because this was a case report in accordance with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards and the ethics committee of Sir Run Run Shaw Hospital, Zhejiang University School of Medicine. The written informed consent was obtained from all of the participants including the family of the patient. All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

Consent for publication
Written informed consent was obtained from the patient for publication of any accompanying images and the details of other clinical information.

Competing interests
The authors declare no competing interests.

Received: 4 October 2023 / Accepted: 27 September 2024
Published online: 07 October 2024

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