CASE REPORT

Rare manifestations in a case of Osler-Weber-Rendu disease

Abhijai Singh,¹ Vikas Suri,² Sanjay Jain,² Subhash Varma²¹Department of Internal Medicine, St Vincent Hospital, Worcester, Massachusetts, USA²Department of Internal Medicine, Postgraduate Institute of Medical Education and Research, Chandigarh, India**Correspondence to**
Dr Abhijai Singh,
abhijaisingh@gmail.com

Accepted 6 December 2014

SUMMARY

Osler-Weber-Rendu disease (OWRD) is a rare vascular dysplasia that presents most commonly with epistaxis. The most dreaded complication, however, is an intracranial haemorrhage. We present a patient with two rare manifestations of OWRD, subdural haematoma and portal venous hypertension, both seldom reported in the literature. The patient made a full recovery and continues to do well at this time.

BACKGROUND

Osler-Weber-Rendu disease (OWRD), or hereditary haemorrhagic telangiectasia (HHT), is an inherited vascular dysplasia transmitted as an autosomal dominant trait with high penetrance and variable expressivity.^{1–2} It is more common than previously estimated with a prevalence of 1–2 cases per 10 000.² Epistaxis is the most common clinical manifestation, present in up to 96% of cases.³ Cutaneous telangiectasias are present in 75% of patients and mostly manifest only in the second or third decade.⁴ The vascular malformations may involve multiple organs including the lung (30%), liver (30%), and kidney and brain (10%). Frameshift mutations in the extracellular part of ENG gene that encodes endoglin, a receptor for transforming growth factor- β 1, are responsible for the most common type of HHT.⁵ Intracranial haemorrhage (ICH) is a rare presentation with an estimated risk of <1%. We present a case with subdural haematoma, which is even more infrequent.

CASE PRESENTATION

A 60-year-old woman presented to our hospital for evaluation of anaemia and recurrent epistaxis. She had a history of two episodes of moderate haematemesis followed by melaena. Upper gastrointestinal endoscopy revealed multiple mucosal punctate lesions symptomatic of telangiectasias in the stomach. There was no associated history of haemoptysis or dyspnoea. Family history revealed presence of a symptomatic individual in every generation of the family but no history suggestive of intracranial manifestations (figure 1).

Two months after her first presentation to our clinic, the patient presented to the emergency room again with profuse epistaxis of 2 days duration. On admission, the patient was conscious, oriented, had tachycardia (heart rate 118/min), was normotensive (110/80 mm Hg) and had a respiratory rate of 16/min. Physical examination revealed pallor and HEENT examination was significant for presence of telangiectasias on the tongue, lips and face

Figure 1 Family tree of the patient.

(figures 2–4). There was active bleeding from the nose. Laboratory investigations revealed significant anaemia with haemoglobin of 4.7 g/dL with presence of microcytosis, anisopoikilocytosis and hypochromia on peripheral smear. Serum electrolytes, liver function and renal function tests were within normal limits. Coagulogram revealed an international normalised ratio of 1.2 and plasma thromboplastin time (PTTK) of 26".

Ultrasound (USG) of the abdomen revealed splenomegaly (14.7 cm) with portal hypertension (portal vein diameter of 14 mm) and multiple areas of vascular calcification in the spleen. Left-sided significant hydronephrosis was also detected. These findings were confirmed by contrast-enhanced CT of the abdomen, which did not reveal any intra-abdominal arteriovenous malformations (AVMs; figure 5). A CT of the chest was negative for any pulmonary AVMs (PAVMs). The patient was managed with anterior nasal packing and three units of packed red blood cells, and underwent septal dermoplasty for recurrent epistaxis. In the

Figure 2 Multiple dilated cutaneous vessels (telangiectasias) present on the volar pads of fingers.

CrossMark

To cite: Singh A, Suri V, Jain S, et al. *BMJ Case Rep* Published online: [please include Day Month Year] doi:10.1136/bcr-2014-207852

Figure 3 Multiple tongue telangiectasias.

Figure 4 Multiple facial telangiectasias.

Figure 5 Contrast-enhanced CT of the abdomen revealed presence of dilated portal vein with mild splenomegaly.

Figure 6 Non contrast CT scan (NCCT) of the brain revealing R frontotemporal concavoconvex hypodense lesion with intermittent hyperdensities suggestive of acute on chronic subdural haematoma.

immediate postoperative period she was found to be drowsy and non-responsive to commands. This was initially attributed to the delayed effect of the anaesthesia, but neuroimaging was ordered when the patient remained non-responsive. CT of the brain without contrast revealed right-sided frontotemporal acute on chronic subdural haematoma with gross midline shift ([figure 6](#)).

TREATMENT

The patient underwent septal dermoplasty for recurrent epistaxis and an emergent evacuation of the subdural haematoma, and was subsequently started on danazol in the postoperative period. Intraoperatively, multiple dural AVMs were identified and clipped.

OUTCOME AND FOLLOW-UP

The patient improved completely. Presently she is on follow-up for the past 4 years, with no residual neurological deficit (modified Rankin scale 0) and no recurrent bleeding episodes on danazol.

DISCUSSION

The diagnosis of OWRD or HHT is based on Curacao clinical criteria which are as follows:⁶

1. Epistaxis;
2. Telangiectasias—characteristic sites include lips, oral cavity, fingers and nose;
3. Visceral lesions including gastrointestinal, hepatic, PAVMs, cerebral AVMs (CAVMs) or spinal AVMs;
4. Family history with a first-degree relative with HHT.

Presence of three criteria makes a definite diagnosis and two are needed for a possible diagnosis.

Our patient had all the four criteria present during the follow-up. This case had an odd presentation in that subdural haematoma as a complication of HHT is very uncommon. Additionally, portal hypertension, though reported without liver disease in these patients, is a rare manifestation.

A review of the literature via PubMed revealed only one infant who developed bilateral subdural haematomas that were secondary to surgical clipping of intracerebral aneurysms. He succumbed to the illness. To our knowledge, this represents the first case of HHT presenting as subdural haematoma with successful resolution of neurological deficits.

In 12–36% of patients with neurological involvement and HHT, vascular malformations of the brain and spinal cord can be documented.^{7–8} Five to 11% of these cerebrovascular malformations are CAVMs. In a large study by Willemse *et al*,⁸ they used intravenous digital subtraction angiography (DSA) to document CAVMs in 11% of 196 patients with HHT. They estimated the risk of bleeding as 0.36–0.56%. This risk has been found to be lower than those with sporadic AVMs. The exact reason for this difference is not known although several possibilities, including younger age group of HHT population, different intrinsic characteristics of HHT AVMs due to hereditary nature of the disease and screening procedure differences have been put forward by the authors. In a study by Maher *et al* involving review of medical records of 321 patients from Mayo clinic, only 12 patients (3.7%) had a history of cerebral vascular malformations. Ten patients had AVMs, one had a dural arteriovenous fistula, and one had a cavernous malformation. Of these, 7 (2.1%) patients presented with ICH, 2 presented with seizures alone and 3 were discovered as an incidental finding during routine screening.⁹ Similar results have been reported in other studies. Willemse *et al* have reported just three cases of ICH in their series of 196 patients (1.5%).⁹ Fulbright *et al*,¹⁰ in their study, had no patient with ICH.

The average age of patients presenting with ICH was in the third decade in the study by Maher *et al*.⁹ Similar results were achieved in multiple case reports and case series with all highlighting the importance of young age at presentation.^{7–11–16} Our *index patient* was in the sixth decade at the time of her initial presentation. It has been hypothesised that presence of CAVM or ICH in a first-degree relative may be a risk factor for similar AVMs in the HHT population. Our patient did not have a family history of neurological manifestations, although a possibility of asymptomatic CAVM cannot be ruled out since none of them had been screened by DSA or MRI.

Neurological manifestations are more common in those with pulmonary arteriovenous fistula (AVF) than in those with cerebrovascular malformations. Maher *et al*⁹ in their study found 71 (22.1%) patients with PAVMs and of these, greater than one-third (36%) of patients had varied neurological manifestations either as cerebrovascular accident (CVA), transient ischaemic attack or ICH. Mechanisms of neurological manifestations other than bleeding include paradoxical emboli with brain abscess, ischaemic stroke, cerebral injury caused by cerebral hypoxia arising from right to left shunting, air embolism and secondary polycythaemia.¹⁷

Given the high frequency of neurological manifestations in those with PAVMs, consideration is given to screening for PAVMs in all patients with neurological involvement.^{18–20} This is done via physical examination, chest X-ray and arterial blood gas analysis to reveal an increased shunt fraction. Patients with orthodeoxia are screened with a contrast ECHO or CT of the chest to establish the presence of PAVMs. All these were within normal limits in the *index case*. This was again an atypical finding in the *index case* considering the high frequency of PAVMs in patients with intracranial AVMs. Selective pulmonary angiography and three-dimensional helical CT scan, though more sensitive, were not performed on the patient due to absence of any abnormal findings on preliminary investigations.

HHT is a common cause of hepatic involvement in the form of focal nodular hyperplasia and hepatic AVMS, more commonly reported with activin receptor-like kinase 1 mutation with a prevalence of up to 84%.^{21–22} However, portal hypertension is uncommon with presence in less than 10% patients.^{21–22} Portal hypertension and hepatic encephalopathy more commonly appear to result from increased sinusoidal blood flow, leading to enhanced deposition of fibrous tissue and pseudo cirrhosis of the liver.^{23–24}

Though not described in our patient, of interest are the ocular manifestations of HHT, which include conjunctival and retinal telangiectasias and recently described choriocapillaris atrophy.^{25–26}

No single specific therapy has been effective, though antioestrogen therapy has been explored in delaying the progression of telangiectasias.^{27–30} Surveillance guidelines include annual investigation for anaemia and a neurological examination.²⁰ Screening for pulmonary artery AVMs is performed every 1–2 years during childhood followed by five yearly examinations after 10–12 years.^{20–31} Initial screening is performed using pulse oximetry in supine and sitting positions. All children with saturation below 97% should have a contrast ECHO performed and positive examinations should be confirmed by a multidetector CT. A detailed review on therapy and follow-up of PAVMs is beyond the scope of this article.

A thorough pedigree analysis and evaluation of the family should be performed. Controversy still exists on routine screening of patients with HHT for CAVMs, which stems from the paucity of studies demonstrating benefit of treatment in asymptomatic CAVMs. At this point, the first international HHT guidelines suggest MRI of the brain at age 18 or at the time of diagnosis and no further screening beyond that if negative. This recommendation is based on expert opinion and warrants further studies for validation.²⁰ Whether a screening would have been appropriate in our case with extraparenchymal CAVMs would be arguable since dural AVMs may be missed on cross-sectional imaging, with digital subtraction angiography being the gold standard for diagnosis.³² This case highlights the need to evaluate for uncommon possibilities in a patient of HHT with neurological compromise and revisits the current understanding on evaluation of a newly diagnosed patient.

Learning points

- ▶ Be aware of the diagnosis of hereditary haemorrhagic telangiectasia (HHT) and its various bleeding manifestations.
- ▶ Neurological manifestations of HHT can be catastrophic and delayed, and can be in the form of intracranial haemorrhage, CVA or subdural haematoma.
- ▶ Awareness of arteriovenous malformations as a cause of portal hypertension (HTN) in these patients is needed.
- ▶ Surveillance guidelines must be followed for patients with HHT.

Competing interests None.

Patient consent Obtained.

Provenance and peer review Not commissioned; externally peer reviewed.

REFERENCES

- 1 Porteous MEM, Burn J, Proctor SJ. Hereditary hemorrhagic telangiectasia: a clinical analysis. *J Med Genet* 1992;29:527–30.

- 2 Garland HG, Annig ST. Hereditary hemorrhagic telangiectasia: genetic and biographical study. *Br J Dermatol* 1950;62:289–310.
- 3 AAssar OS, Friedman CM, White RI. The natural history of epistaxis in hereditary hemorrhagic telangiectasia. *Laryngoscope* 1991;101:977–80.
- 4 Peery WH. Clinical spectrum of hereditary hemorrhagic telangiectasia (Osler-Weber-Rendu disease). *Am J Med* 1987;82:989–98.
- 5 McAllister KA, Grogg KM, Johnson DW, et al. Endoglin, a TGF-beta binding protein of endothelial cells, is the gene for hereditary hemorrhagic telangiectasia type 1. *Nat Genet* 1994;8:345–51.
- 6 Shovlin CL, Guttmacher AE, Buscarini E, et al. Diagnostic criteria for hereditary hemorrhagic telangiectasia (Rendu-Osler-Weber syndrome). *Am J Med Genet* 2000;91:66–7.
- 7 Roman G, Fisher M, Perl DP, et al. Neurological manifestations of hereditary hemorrhagic telangiectasia (Rendu-Osler-Weber disease): report of 2 cases and review of the literature. *Ann Neurol* 1978;4:130–44.
- 8 Willemse RB, Mager JJ, Westermann CJ, et al. Bleeding risk of cerebrovascular malformations in hereditary hemorrhagic telangiectasia. *J Neurosurg* 2000;92:779–84.
- 9 Maher CO, Piepgras DG, Brown RD, et al. Cerebrovascular manifestations in 321 cases of hereditary hemorrhagic telangiectasia. *Stroke* 2001;32:877–82.
- 10 Fulbright RK, Chaloupka JC, Putman CM, et al. MR of hereditary hemorrhagic telangiectasia: prevalence and spectrum of cerebrovascular malformations. *AJNR Am J Neuroradiol* 1998;19:477–84.
- 11 Kadoya C, Momota Y, Ikegami Y, et al. Central nervous system arteriovenous malformations with hereditary hemorrhagic telangiectasia: report of a family with three cases. *Surg Neurol* 1994;42:234–9.
- 12 Kikuchi K, Kowada M, Sasajima H. Vascular malformations of the brain in hereditary hemorrhagic telangiectasia (Rendu-Osler-Weber disease). *Surg Neurol* 1994;41:374–80.
- 13 Hanieh A, Blumbergs PC, Carney PG. Multiple cerebral arteriovenous malformations associated with soft tissue vascular malformations. *J Neurosurg* 1981;54:670–2.
- 14 Waller JD, Greenberg JH, Lewis CW. Hereditary hemorrhagic telangiectasia with cerebrovascular malformations. *Arch Dermatol* 1976;112:49–52.
- 15 Willinsky RA, Lasjaunias P, Terbrugge K, et al. Multiple cerebral arteriovenous malformations (AVMs): review of our experience from 203 patients with cerebral vascular lesions. *Neuroradiology* 1990;32:207–10.
- 16 John PR. Early childhood presentation of neurovascular disease in hereditary hemorrhagic telangiectasia. *Pediatr Radiol* 1992;22:140–1.
- 17 Putman CM, Chaloupka JC, Fulbright RK, et al. Exceptional multiplicity of cerebral arteriovenous malformations associated with the hereditary hemorrhagic telangiectasia (Osler-Weber-Rendu syndrome). *AJNR Am J Neuroradiol* 1996;17:1733–42.
- 18 Kjeldsen AD, Oxhøj H, Andersen PE, et al. Pulmonary arteriovenous malformations: screening procedures and pulmonary angiography in patients with hereditary hemorrhagic telangiectasia. *Chest* 1999;116:432–9.
- 19 Parra JA, Bueno J, Zarauza J, et al. Graded contrast echocardiography in pulmonary arteriovenous malformations. *Eur Respir J* 2010;35:1279–85.
- 20 Faughnan ME, Palda VA, Garcia-Tsao G, et al. International guidelines for the diagnosis and management of hereditary hemorrhagic telangiectasia. *J Med Genet* 2011;48:73–87.
- 21 Buonamico P, Suppressa P, Lenato GM, et al. Liver involvement in a large cohort of patients with hereditary hemorrhagic telangiectasia: Echo-color-Doppler vs multislice computed tomography study. *J Hepatol* 2008;48:811–12.
- 22 Ianora AA, Memeo M, Sabba C, et al. Hereditary hemorrhagic telangiectasia: multi-detector row helical CT assessment of hepatic involvement. *Radiology* 2004;230:250–9.
- 23 Garcia-Tsao G, Korzenik JR, Young L, et al. Liver disease in patients with hereditary hemorrhagic telangiectasia. *N Engl J Med* 2000;343:931.
- 24 Saluja S, White RI. Hereditary hemorrhagic telangiectasia of the liver: hyperperfusion with relative ischemia—poverty amidst plenty. *Radiology* 2004;230:25.
- 25 Geischoff UW, Hille K, Ruprecht KW, et al. Prevalence of ocular manifestations in hereditary hemorrhagic telangiectasia. *Graefes Arch Clin Exp Ophthalmol* 2007;45:1141–4.
- 26 Rinaldi M, Buscarini E, Chiosi F, et al. Ocular manifestations in hereditary hemorrhagic telangiectasia (Rendu-Osler-Weber disease): a case-series. *Ophthalmic Genet* 2011;32:12–7.
- 27 Govani FS, Shovlin CL. Hereditary hemorrhagic telangiectasia: a clinical and scientific review. *Eur J Hum Genet* 2009;17:860–7.
- 28 Lund VJ, Howard DJ. A treatment algorithm for the management of epistaxis in hereditary hemorrhagic telangiectasia. *Am J Rhinol* 1999;13:319–22.
- 29 Hitchings AE, Lennox PA, Lund VJ, et al. The effect of treatment for epistaxis secondary to hereditary hemorrhagic telangiectasia. *Am J Rhinol* 2005;19:75–8.
- 30 Yaniv E, Preis M, Hadar T, et al. Antiestrogen therapy for hereditary hemorrhagic telangiectasia: a double-blind placebo-controlled clinical trial. *Laryngoscope* 2009;119:284–8.
- 31 McDonald J, Bayrak-Toydemir P, Pyeritz RE. Hereditary hemorrhagic telangiectasia: an overview of diagnosis, management, and pathogenesis. *Genet Med* 2011;13:607–16.
- 32 Geibprasert S, Pongpech S, Jiarakongmun P, et al. Radiologic assessment of brain arteriovenous malformations: what clinicians need to know. *Radiographics* 2010;30:483–501.

Copyright 2015 BMJ Publishing Group. All rights reserved. For permission to reuse any of this content visit <http://group.bmj.com/group/rights-licensing/permissions>.
BMJ Case Report Fellows may re-use this article for personal use and teaching without any further permission.

Become a Fellow of BMJ Case Reports today and you can:

- Submit as many cases as you like
- Enjoy fast sympathetic peer review and rapid publication of accepted articles
- Access all the published articles
- Re-use any of the published material for personal use and teaching without further permission

For information on Institutional Fellowships contact consortiasales@bmjgroup.com

Visit casereports.bmj.com for more articles like this and to become a Fellow