



A Rare Case of Hht (Osler Weber Rendu Syndrome) With Recurrent Epistaxis

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ABSTRACT

A middle aged male patient was admitted in our medical ward with complaints of recurrent epistaxis for the past three years. History revealed that he had haemangiomas spread throughout his body, especially over the lips, tongue, buccal mucosa & bulbar conjunctiva. His Family history is positive with his father having had similar complaints & his grand daughter with mild epistaxis. His hematological evaluation showed severe microcytic, hypochromic anaemia and raised Liver function tests. USG Abdomen showed moderate hepatosplenomegaly with portal cavernoma. UGIE & Colonoscopy done which revealed multiple telangiectasias over tongue & palate & all over colon with maximum number in Caecum. Diagnosis is made clinically based on Curacao criteria as a case of Hereditary Hemorrhagic Telangiectasia (Osler Weber Rendu syndrome). The Genetic probability, pathophysiology, clinical features & management are discussed and literature is reviewed.

KEYWORDS

Epistaxis, Visceral Telangiectasias, anaemia, family history

INTRODUCTION:

Hereditary Haemorrhagic Telangiectasia (HHT), also known as Osler-Rendu-Weber disease, is rare and an autosomal dominant vascular disease. Epistaxis may begin in childhood or later in adolescence. Punctate telangiectasias of the lips, tongue, fingers and skin generally appear in later childhood and adolescence. The vascular malformations are arteriovenous shunts termed telangiectasias (if small), or arteriovenous malformations (if large). Skin lesions are papular. Clinical manifestations depend on the organ involved. Bleeding from GIT is due to vascular malformation and usually not a problem until middle adult years or later. Pulmonary AVMs can cause hypoxemia and right-to-left shunting (with embolic strokes or brain abscess). Four diagnostic criteria for HHT have been established: (i) epistaxis; (ii) telangiectasias on the face, fingertips, nasal and oral mucosa; (iii) a family history of HHT; (iv) visceral lesions including gastrointestinal telangiectasias, pulmonary arteriovenous malformations (PAVMs), cerebral arteriovenous malformations (CAVMs), spinal arteriovenous malformations and hepatic vascular malformations. The diagnosis of HHT is considered definite if at least three of these criteria are present, suspected if two are present, and unlikely if only one is present. Mutation analysis can be used for presymptomatic diagnosis or exclusion of the worry of HHT.

CASE REPORT

A 38 year old male patient, Mr. Arun Chowdary came to the General Medicine Department of GGH, Vijayawada, complaining of recurrent Epistaxis for the past 3 years with aggravation over the past one month, having had bleeding episodes of more than 3/day.

For about 15 years he had haemangiomas spread throughout his body, especially over the lips, tongue, buccal mucosa & bulbar conjunctiva. He was normotensive, non-diabetic, non-smoker, non-alcoholic. Family history was positive with his father having had recurrent episodes of epistaxis, however milder than this patient and with the telangiectasis on his skin and mucosa. He has a grand daughter, 18 year old with mild epistaxis.

General and Physical examination : We noticed telangiectatic lesions spread throughout his lips, tongue, buccal mucosa, bulbar conjunctiva & nail beds. He is conscious, coherent & afebrile and no neurological focal deficits. Vitals are : pulse rate of 94/min, blood pressure of 120/70 mm Hg, respiratory rate of 18/min. Pallor present & no cyanosis. Cardiovascular and Respiratory system examination is normal. Other findings include moderate Hepatosplenomegaly.

Hemogram showed a picture of severe microcytic, hypochromic anaemia with severe erythropenia, Hb of 4.3 gm %, hematocrit of 10.4%, WBCs & platelets are adequate. Coagulation profile & Liver function tests done : BT – 2 min 15 secs, CT – 5 min 30 secs, Fibrinogen – 385 mg% (150-400), vWF – 13.5%, Ferritin – 44.8 ng/dl, Iron – 112 microg/dl, TIBC – 295 microg/dl, vit B12 – 215 pg/ml, Total Bilirubin – 4.4 mg% (D-3, ID 1.4), SGOT – 110 U/L, SGPT – 179 U/L, ALP – 70 U/L, Total protein – 5.7 gm/dl, Albumin – 2.9 gm/dl with A/G ratio of 1.03, PT – INR Test – 17 secs, Control – 13 secs, INR – 1.5. Other investigations include Sr. Creatinine – 0.6 mg/dl. HIV, HBsAg and HCV are Non reactive.

Radiological investigations showed as such:

UGI Endoscopy – Oral cavity – full of Telangiectasias over tongue and palate with Bleeding lesion in 2nd part of Duodenum

USG Abdomen – Moderate Hepatosplenomegaly with portal cavernoma and no ascites

Colonoscopy – In general, mucosa is bluish in colour. There are multiple telangiectasias all over Right Ascending colon, descending colon with maximum in Caecum

The Clinical, Radiological and Haematological picture, confirmed the patient as a case of Hereditary Hemorrhagic Telangiectasia, and the Diagnosis is mostly clinical, based on Curacao criteria, established by the Scientific division of The Hereditary Hemorrhagic Telangiectasia International Foundation.

Patient is treated as per the protocol & discharged in a stable condition & reviewed regularly.



DISCUSSION :

The presentation of HHT can be highly variable among families and even within the same family. Cutaneous findings may be subtle; epistaxis, the most common overt feature, is also common in the general population. There is no firm consensus on the number of episodes or degree of epistaxis necessary for diagnosis; according to the Curaçao criteria, nosebleeds should occur spontaneously on more than 1 occasion, and night-time bleeding should be considered as suspicious of HHT.

Five genetic types of HHT are recognized. Of these, three have been [linked](#) to particular [genes](#), while the two remaining have currently only been associated with a particular [locus](#). More than 80% of all cases of HHT are due to mutations in either ENG or ALK-1 and SMAD4.

Genetic testing of OWRD patients and their family members can confirm the presence of mutations within implicated genes, most commonly the endoglin gene (*ENG*) in chromosome 9 or the activin receptorlike kinase type I gene (*ALK1*) in chromosome 12 (involved in HHT type 1 and type 2, respectively). Both ENG and ALK-1 encode putative receptors for the transforming growth factor-beta (TGF- β) superfamily that play a critical role for the proper development of the blood vessels. Mutations in Smad4 have also been identified in a subset of patients with a combined syndrome of HHT and juvenile poliposis.

Screening family members for signs of OWRD is reasonable and should include a complete history, physical examination, radiological, and arterial blood gas testing (with measurement of the shunt fraction).

All [genes](#) known so far to be linked to HHT code for proteins in the [TGF- signaling pathway](#). This is a group of proteins that participates in [signal transduction](#) of hormones of the [transforming growth factor beta super family](#) (the [transforming growth factor beta](#), [bone morphogenetic protein](#) and [growth differentiation factor](#) classes), specifically [BMP9/GDF2](#) and [BMP10](#). The hormones do not enter the cell but link to receptors on the cell membrane; these then activate other proteins, eventually influencing cellular behavior in a number of ways such as cellular survival, proliferation (increasing in number) and differentiation (becoming more specialized). For the hormone signal to be adequately transduced, a combination of proteins is needed: two each of two types of [serine/ threonine - specific kinase type membrane receptors](#) and endoglin. When bound to the hormone, the type II receptor proteins phosphorylate (transfer [phosphate](#)) onto type I receptor proteins (of which Alk-1 is one), which in turn phosphorylate a complex of [SMAD proteins](#) (chiefly [SMAD1](#), [SMAD5](#) and [SMAD8](#)). These bind to SMAD4 and migrate to the [cell nucleus](#) where they act as [transcription factors](#) and participate in the [transcription](#) of particular genes. In addition to the SMAD pathway, the membrane receptors also act on the [MAPK pathway](#), which has additional actions on the behavior of cells. Both Alk-1 and endoglin are [expressed](#) predominantly in endothelium, perhaps explaining why HHT-causing mutations in these proteins lead predominantly to blood vessel problems. Both ENG and ACVRL1 mutations lead predominantly to underproduction of the related proteins, rather than malfunctioning of the proteins. Telangiectasias and arteriovenous malformations in HHT are thought to arise because of changes in [angiogenesis](#). The wall of telangiectasias is unusually [friable](#), which explains the tendency of these lesions to bleed.

The diagnosis of Osler-Weber-Rendu disease (OWRD; ie, hereditary hemorrhagic telangiectasia [HHT]), is made clinically on the basis of the Curaçao criteria, established in June 1999 by the Scientific Advisory Board of the HHT Foundation International, Inc, for the purposes of improving patient care and standardizing research.^[9] These criteria are as follows:

1. Epistaxis - Spontaneous and recurrent
2. Telangiectases - Multiple characteristic sites (eg, lips, oral cavity, fingers, or nose)
3. Visceral lesions - Gastrointestinal (GI) telangiectasia (with or without bleeding), [pulmonary arteriovenous malformation \(AVM\)](#), hepatic AVM, [cerebral AVM](#), and spinal AVM
4. Family history - A first-degree relative who has HHT (according to these same criteria)

The HHT diagnosis is classified as definite if 3 criteria are present, possible or suspected if 2 criteria are present, and unlikely if fewer than 2 criteria are present. There is no firm consensus on the number of episodes or degree of epistaxis necessary for diagnosis; according to the Curaçao criteria, nosebleeds should occur spontaneously on more than 1 occasion, and night-time bleeding should be considered especially suspicious

Overall, life expectancy appears to be shortened by OWRD (HHT) ; nevertheless, with appropriate screening and aggressive management, life expectancy for the majority of patients may approach that of the normal population. Mortality shows an early peak at age 50 years and a later peak at 60-79 years related to acute complications.

The prognosis is highly dependent on the severity of the disease—in particular, on the degree of systemic involvement, especially pulmonary, hepatic, and central nervous system (CNS) involvement. Only 10% of patients die of complications of HHT.

The prevalence of brain AVM in HHT1 patients is 1000-fold higher and in HHT2 100-fold higher than the prevalence in the general population (10 in 100,000). Pulmonary and CNS arteriovenous aneurysms may appear later in life. Patients with pulmonary AVMs and telangiectasis of the GI tract are at risk for life-threatening hemorrhage of the lungs and GI tract. Other sites of bleeding may include sites in the kidney, spleen, bladder, liver, meninges, and brain.

Strokes may be either hemorrhagic or ischemic. Of patients who have pulmonary AVMs, 2% per year are estimated to have a stroke, and 1% per year are estimated to develop a brain abscess. Retinal arteriovenous aneurysms occur only rarely. Patients are also at risk for high-output cardiac failure, migraines and further sequelae.

Frequent nosebleeds and melena may result from telangiectasia in the nose and GI tract. Patients with the severe form of HHT have heavy bleeding and resultant iron-deficiency anemia. Recurrent epistaxis is observed in as many as 90% of patients. In half the patients, the epistaxis becomes more serious with age, and blood transfusions are required in 10-30% of patients.

Epistaxis is often recurrent, necessitating multiple treatments. Moderate and mild epistaxis can be treated medically or with endoscopic ablation.

Nonoperative treatment of epistaxis may include the following:

- Iron supplementation
- Humidification
- Packing

- Transfusion
- Estrogen therapy
- Aminocaproic acid
- Electrocautery and argon beam ablation
- Neodymium:yttrium-aluminum-garnet (Nd:YAG) laser ablation^[104]
- Thalidomide

In more severe cases, iron replacement may be indicated because of blood loss. Humidification of the ambient air helps decrease the amount of mucosal bleeding. Hormone therapy, including antiestrogen therapy with tamoxifen, for the treatment of epistaxis due to HHT has produced good responses, though its use remains controversial. Antifibrinolytics (eg, aminocaproic acid) may be used to enhance hemostasis when fibrinolysis contributes to bleeding.

Pulsed dye laser treatment may be used to photocoagulate telangiectasias in the nasal mucosa. As many as 3 subsequent treatments may be necessary before any change in bleeding frequency or severity is observed.

Future research should be directed toward identifying the minimum dose of thalidomide effective in long-term control of bleeding symptoms in HHT patients without inducing thrombotic adverse events. It appears to be a potential candidate for the treatment of severe HHT-associated epistaxis unresponsive to conventional therapies.

Endovascular embolization for treatment of severe acute epistaxis is another treatment modality that may be considered.

N-acetylcysteine has been studied as an option for management of recurrent epistaxis in patients with HHT. Multiple case reports have illustrated the use of bevacizumab in the treatment of HHT, and the efficacy of this agent for the management of epistaxis in HHT is being studied.

Similar management protocols also holds good for Non-operative management of GIT bleeding.

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