ANAESTHESIA, PAIN & INTENSIVE CARE
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REVIEW ARTICLE

Hereditary hemorrhagic telangiectasia and the anesthesiologist

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Received: 5 Mar 2017
Reviewed & Accepted: 16 Mar 2017

ABSTRACT

Osler-Weber-Rendu disease (OWRD) or Hereditary Hemorrhagic Telangiectasia (HHT) is a rare autosomal dominant disorder that causes muco-cutanesous and visceral vascular dysplasia and results in increased tendency for bleeding. Patients with HHT presenting with continuous bleeding pose a serious problem to the Anesthesiologist .Pre-existing anemia due to recurrent bleeding is common and sudden decompensation may lead to heart failure. Uncontrolled bleeding may occur from skin lesions during patient positioning and transport. Epistaxis may lead to aspiration of blood into trachea causing pulmonary edema. Intravenous access may be difficult. Sudden change in blood pressure may cause bleeding from arteriovenous malformations (AVMs) anywhere in the body, most serious of which is from cerebral AVM. Gastric distension may occur from ingested blood and may cause reflux and aspiration during induction. Any instrumentation including laryngoscopy and intubation, nasogastric tube insertion, urinary catheterization should be carried out with utmost caution as bleeding may occur from undetected lesions. Management include blood transfusion, antifibrinolytics and surgical hemostasis. Anesthesia strategy should include rapid sequence induction and controlled hypotension.

Key words: Telangiectasia, Hereditary Hemorrhagic; Osler-Rendu Disease; Osler-Weber-Rendu Syndrome; Congenital Abnormalities; Cardiovascular Abnormalities; Vascular Malformations; Arteriovenous Malformation

Citation: Kar SK, Ganguly T. Hereditary hemorrhagic telangiectasia and the anesthesiologist. Anaesth Pain & Intensive Care 2017;21(3):387-392

INTRODUCTION

Osler-Weber-Rendu disease (OWRD) or Hereditary Hemorrhagic Telangiectasia (HHT) is a rare autosomal dominant disorder that causes muco-cutanesous and visceral vascular dysplasia and results in increased tendency for bleeding[1-4]. Patients with HHT may present with variety of symptoms and management differs accordingly. Epistaxis is the most common symptom of HHT and mucocutaneous telangiectasia is the most common sign[5].

INCIDENCE

HHT is a rare systemic fibro vascular dysplasia[6] with incidence varying from 1 in 5,000 to 10,000[7] to 1 to 2 in 1,00,000[6]. Sutton[8] in 1864 first described this syndrome in a man with a vascular malformation and recurrent epistaxis. In 1896 Rendu[9] first noted the association between hereditary epistaxis and telangiectasia in a 52 years old man. Osler[10] in 1901 and Weber[11] in 1907 further elaborated the association between hemorrhagic lesions in skin and mucous membranes and its familial inheritance. Although

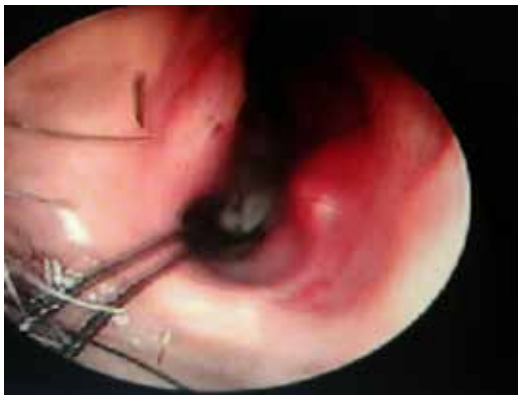

Figure 1: Endoscopic view of the angiofibroma

the disease is popularly known as Osler-Weber-Rendu syndrome, the name 'hereditary hemorrhagic telangiectasia' suggested by Hanes[12] in 1909, recognizes the characteristics that define the disease.

GENETICS OF HHT

HHT is manifested by mucocutaneous telangiectasias and arteriovenous malformations (AVMs) in different parts of body. Lesions can affect the nasopharynx, central nervous system (CNS), lung, liver, and spleen, as well as the urinary tract, gastrointestinal (GI) tract, conjunctiva, trunk, arms, and fingers.[2,13] Impaired signaling of transforming growth factor-ß/bone morphogenesis protein (TGF-β/BMP)[14-17] as well as vascular endothelial growth factor (VEGF)[18,19] has been attributed as the primary cause of HHT. The gene mutations found to be responsible are as follows in Table 1.

DIAGNOSIS

The diagnosis of HHT is made clinically on the basis of the Curaçao criteria[3], established in June 1999 by the Scientific Advisory Board of the HHT Foundation International, Inc. (Table 2), and recommended by HHT Foundation International - Guidelines Working Group,[33] or by identification of a causative mutation.

Histopathology of HHT lesions show many layers of smooth muscle cells without elastic fibers and very frequently arterioles directly communicating with smooth muscle cells. As a result telangiectasias are very sensitive to slight trauma and friction. HHT may present in children as bleeding but usual age of presentation in adulthood[4]. Male and females are equally affected[34]. Classic triad of presentation include telangiectasias of the skin and mucous membranes, epistaxis, and a positive family history. Epistaxis may be present in upto 95% cases[4,35] whereas skin lesions account for 75-90% of presentations[35,36]. Skin telangiectasias rarely cause bleeding[4.] Gastrointestinal telangiectasia may occur in 10-33% patients[37] most commonly in the stomach and upper duodenum[37]. Significant bleeding from gastrointestinal tract may occur in 25% patients older than 60 years and may increase with age[38]. Pulmonary involvement in the form of arteriovenous malformations (AVMs) may be present in 75% HHT1 and 44% HHT2 patients[39]. Patients with pulmonary involvement are at high risk of developing cerebral thrombotic and embolic events including stroke, brain abscess, or transient ischemic attacks due to right-to-left shunting[14,37]. Cerebral AVMs may be present 15-20% HHT1 and 1-2% HHT2 patients[39-43], and may present with seizure, headache or intracranial haemorrhages[4,44]. Hepatic AVMs may be present upto 74% cases[45] but usually asymptomatic[4].

MANAGEMENT

Management strategies for AVMs associated with HHT may differ with location and presentation and depicted in Table 3.

Table 1: Types of HHT with genetic basis

HHT types	Mutated genes	Gene location
HHT1	ENG[20]	Long arm of chromosome 9[21-23]
HHT2	ALK1 (Activin receptor-like kinase 1), also called ACVRL1[24,25]	Long arm of chromosome 12
hereditary benign telangiectasia (HBT), HHT3	RASA1 [26]	chromosome 5q14
HHT4		Chromosome 7p14[27]
HHT + Juvenile polyposis coli	SMAD4/MADH4[28-30]	18q21.2
HHT2 + primary pulmonary hypertension	BMPRII[31,32]	2q33

Table 2: Curaçao criteria

Criterion	Description
Epistaxis	Spontaneous and recurrent
Telangiectasias	Multiple, at characteristic sites: lips, oral cavity, fingers, nose
Visceral lesions	GI Telangiectasia, pulmonary, hepatic, cerebral or spinal AVMs
Family history	A first degree relative with HHT according to these criteria

"definite" if 3 or more criteria are present, "possible or suspected" if 2 criteria are present, and "unlikely" if 0 or 1 criterion is present.

Table 3: Management strategy of HHT according to site of involvement

Location	Lesions	Indications of management	Management
Nose	Telangiectasia, AVMs	Recurrent epistaxis	Sclerotherapy with sodium tetradecyl sulphate[46], submucosal radiofrequency[47], Bevacizumab[48], Septal mucosal dermoplasty[39,49], Embolization of external carotid artery branches[50],
Skin	Telangiectasia	Pain[2], cosmesis[4]	Cauterization, hypertonic saline sclerotherapy, dye laser treatment[51]. Pulsed Nd:YAG laser[52],
Gastro intestinal tracts	AVMs, Angio-dysplasia[4]	Chronic anemia, melena	Diagnosis: Endoscopy, Angiography[4] Management: Bipolar electrocoagulation[4], Laser[4], estrogen-progesterone therapy[53], interferon □[54]
Lungs	AVMs	Exercise intolerance, cyanosis, migraine headaches, polycythemia and clubbing CNS events[14,40] During pregnancy[55]	Feeder vessel >3 mm: Transcatheter embolisation[56], Smaller lesion: Follow up[14] Antibiotic prophylaxis to prevent brain abscess
	Diffuse pulmonary AVM	Severe hypoxia	Lung transplantation[4]
CNS	Cerebral and spinal AVMs		Transcatheter embolization, resection, stereotactic radiosurgery[57,58]
Liver	AVMs,	Life threatening portosystemic shunts	Liver transplant[59-61] Bevacizumab[62]

Patients with HHT presenting with continuous bleeding pose a serious problem to the Anesthesiologist .Pre-existing anemia due to recurrent bleeding is common and sudden decompensation may lead to heart failure. Uncontrolled bleeding may occur from skin lesions during patient positioning and transport. Epistaxis may lead to aspiration of blood into trachea causing pulmonary edema. Intravenous access may be difficult. Sudden change in blood pressure may cause bleeding from AVMs anywhere in the body, most serious of which is from cerebral AVM. Gastric distension may occur from ingested blood and may cause reflux and aspiration during induction. Any instrumentation including laryngoscopy and intubation, nasogastric tube insertion, urinary catheterization should be carried out with utmost caution as bleeding may occur from undetected lesions.

Box 1: Perioperative management problems in HHT patient

Perioperative management risk and problems

1. **Patient may present with:**
   - Preexisting anemia
   - AVMs elsewhere
   - Blood in stomach
   - Aspiration
2. **Surgery related:**
   - Difficult exposure
   - Difficult hemostasis
   - Prolonged surgery
3. **Problems in anesthesia conduct:**
   - Positioning and transport
   - Perioperative aspiration risk
   - Unstable hemodynamics
   - IV access
   - Instrumentation
   - Massive blood transfusion

In hemodynamically stable patients, posted for elective surgery, preoperative optimization of the anemic status is corrected with oral or parenteral iron and if necessary erythropoiesis-stimulating agent[63]. Preoperatively angiogenesis inhibitors or hormone therapy should be considered in selected patients to reduce perioperative bleeding. Careful history and physical examination may indicate any systemic involvement and standard radiological imaging with angiography may be performed to search for hemangiomas in brain, lung, gastrointestinal tract, nose and paranasal sinuses. In unstable patient presenting with severe bleeding focus should be directed to simultaneous resuscitation and hemostasis. Blood transfusion forms the mainstay of volume resuscitation in severely volume depleted patient. Epistaxis should be controlled with tight nasal packing immediately followed by cauterization of bleeding vessels and Septodermoplasty if required. Since bleeding does not result from a defect in coagulation cascade, but from the malformed vascular structures, platelet or

plasma transfusions are of no use and reserved only to supplement the loss. Antifibrinolytics including tranexamic acid[64,65] and aminocaproic acid[66] have been used with success to control epistaxis. In addition to antifibrinolytic effects, tranexamic acid also stimulates the expression of ALK-1 and endoglin, as well as the activity of the ALK-1/endoglin pathway[67]. Intraoperatively controlled hypotension should be achieved with nitroglycerine or inhaled anesthetics or alpha 2 agonists to reduce bleeding.

CONCLUSION

Patients with Osler-Weber-Rendu disease (OWRD) or Hereditary Hemorrhagic Telangiectasia (HHT) may present with uncontrolled bleeding. Resuscitation along with hemostasis forms the cornerstone of treatment. As the bleeding occurs from malformed vessels, standard coagulation tests will reveal no abnormality. Management strategies include blood transfusion, antifibrinolytics and surgical hemostasis. Anesthesia planning should include rapid sequence induction and controlled hypotension.

Conflict of interest: None declared by the authors

Authors' Contribution:
SKK: Concept and writing
TG: Contributing author

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