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ORIGINAL ARTICLE

Management of patients with hereditary hemorrhagic telangiectasia undergoing general anesthesia: a cohort from a single academic center's experience

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Abstract
Purpose Hereditary hemorrhagic telangiectasia is a rare autosomal dominant disease characterized by capillary malformation leading to multisite cutaneomucosal telangiectasias and multiorgan arteriovenous malformations, which can present challenges to anesthetic care. The primary aim of this report is to present a large cohort of patients with hereditary hemorrhagic telangiectasia undergoing general anesthesia at our institution in regard to comorbid conditions and complications of surgical and anesthetic management.
Methods A computerized search from January 1, 2002 through December 31, 2011 of the Mayo Clinic medical records database was performed for patients with hereditary hemorrhagic telangiectasia who underwent general anesthesia. Medical records were reviewed. Eligibility criteria included patients with definite or suspected hereditary hemorrhagic telangiectasia based on the Curacao diagnostic criteria who underwent general anesthesia during the study period.
Results We identified 74 patients with hereditary hemorrhagic telangiectasia who underwent 163 surgeries. The majority had pulmonary arteriovenous malformations (56.7 %) and iron deficiency anemia (64.7 %), and high levels of disease burden with a median American Society of Anesthesiologist Physical Status score of 3. Most surgeries were related to treating conditions associated with hereditary hemorrhagic telangiectasia, with the majority being procedures to the nasal mucosa for recurrent epistaxis (47.2 %). A sizeable proportion of procedures to the nasal mucosa required transfusion of blood (12/77). One case of epistaxis required 11 units of blood until it was successfully controlled. Another notable complication included migration of a coil to pulmonary arteriovenous malformations into the cerebral circulation.
Conclusion Surgical patients with hereditary hemorrhagic telangiectasia often present with multiorgan involvement. The anesthesia provider needs to be aware of the high prevalence of pulmonary arteriovenous malformations, which may be asymptomatic but can lead to embolic complications. Hemorrhage from epistaxis can be severe, and relatively focal procedures to the nasal mucosa can require blood transfusions.

Keywords Hereditary hemorrhagic telangiectasia · General anesthesia · Perioperative outcomes

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Introduction

Hereditary hemorrhagic telangiectasia (HHT; Osler–Weber–Rendu syndrome) is an inherited vascular disorder characterized by multiple telangiectases and arteriovascular malformations (AVM) [1]. Telangiectases typically involve the lips, face, and fingers as well as nasal, oral, and gastrointestinal mucosa. Repeated bleeding from the telangiectases can be problematic for some patients with frequent epistaxes and bleeding from the gastrointestinal track. Larger AVMs can affect multiple organ systems, typically the lung [2], liver [3], and central nervous system [4]. In addition to bleeding, larger AVMs can result in pulmonary shunting, pulmonary hypertension, high output

cardiac failure, embolic complications, brain abscesses, and liver dysfunction or even hepatic failure. Management of the sequelae of HHT may require surgical intervention. However, given that HHT is rare, a large prospective study to define the risks of anesthesia has never been attempted. To further assess anesthesia outcomes in patients with HHT, we used the Mayo Clinic medical records database to identify patients with HHT who underwent surgery under general anesthesia and reviewed their anesthetic course. In addition, we reviewed comorbidities associated with our HTT patients, as well as major complications that may arise from anesthetic management of patients with HTT.

Methods and materials

This study was approved by the Institutional Review Board of the Mayo Clinic, Rochester MN, USA. Consistent with Minnesota Statute 144.335 Subd. 3a.(d), we included only patients who have provided authorization for research use of their medical records (historically >95 % of Mayo Clinic patients) [5]. A computerized search of the Mayo Clinic Rochester electronic medical records database from January 1, 2002 through December 31, 2011 was conducted to identify patients with the diagnosis of definite or suspected hereditary hemorrhagic telangiectasia (HHT) who underwent general anesthesia at the Mayo Clinic. Diagnosis of HHT was based on the Curacao diagnostic criteria [6, 7]. Patient medical, surgical, and anesthetic records were reviewed for existing comorbid conditions with special emphasis on disease processes associated with HHT as well as perioperative complications that could arise from those conditions. Overall physical status was assessed by the American Society of Anesthesiologist Physical Status (ASA-PS), which was assigned at the time of surgery by the attending anesthesiologist. All data were abstracted from the electronic medical records and entered manually into the web-based Research Electronic Data Capture (REDCap) system (Version 3.6.7; Vanderbilt University, Nashville, TN, USA) [8]. Descriptive summarization of demographic, epidemiological, and other data was performed with continuous variables expressed as mean ± standard deviation or median (range); frequency percentages were used for categorical variables. Two-tailed p values ≤ 0.05 were considered statistically significant.

Results

From July 1, 2002 to June 30, 2012, we identified 74 patients diagnosed with definite or probable hereditary hemorrhagic telangiectasia (HHT) who underwent 163 surgical procedures. Patients had a high burden of disease as evidenced by the median ASA score of 3 [2, 4], with sequelae of HHT being the major contributor to morbidity (Table 1). Most surgeries in this cohort were directly related to treating conditions associated with HHT, with the majority being procedures to the nasal mucosa for recurrent epistaxis (Table 2). Per study definition, all surgeries were performed under general anesthesia; additionally, 3 patients underwent five surgeries under general anesthesia, supplemented by a neuroaxial block for postoperative analgesia. Airway management was uncomplicated via direct laryngoscopy, except for 1 patient who underwent fiberoptic intubation on two different surgeries without clearly documented explanation for the use of this technique. No airway traumas or bleeding were recorded. There were no intraoperative deaths or resuscitative measures beyond expected management for the corresponding surgeries. Almost half (12/25) of blood transfusions were administered during procedures for epistaxis (Table 3). Four patients undergoing nasal surgeries required admission to the intensive care unit. Two patients not undergoing nasal procedures developed epistaxis that required intervention, including a patient who required 11 units of packed red cells and coiling of a nasal AVM. Three serious postoperative complications related to the procedure were noted: one of these was migration of a coil deployed into a pulmonary arteriovenous malformation into the cerebral vasculature.

Discussion

Hereditary hemorrhagic telangiectasia is a vascular disorder characterized by incomplete capillary development resulting in cutaneomucosal telangiectases and larger AVMs that can affect multiple organ systems. HHT has an autosomal-dominant inheritance with varying penetrance caused by mutations of the transforming growth factor-beta/bone morphogenetic protein (TGF-β/BMP) signaling pathway, with the most common being the ENG gene on chromosome 9 for HHT type 1 and ACVRL1 (ALK1) gene on chromosome 12 type 2 [9, 10]. Interestingly, there is an association with juvenile polyposis, another autosomal dominant disorder secondary to a mutation of SMAD4 gene (also part of the TGF-β/BMP signaling pathway) and HHT, and these patients are at higher risk of gastrointestinal malignancies [11]. Diagnosis is made using the Curacao diagnostic criteria, which consist of four components: (1) spontaneous and recurrent epistaxis; (2) multiple mucocutaneous telangiectases of the lips, oral cavity, fingers, or nose; (3) visceral AVM; and (4) family history of a first-degree relative with HHT [6, 7]. Patients with two findings have possible or suspected HHT, and those with three findings have definite HHT. Symptoms of the

Table 1 Characteristics and comorbidities of patients with hereditary hemorrhagic telangiectasia (HHT) undergoing general anesthesia

	Patients ($n = 74$)
Male sex	30 (40.5)
Body mass index (kg m^{-2})	26.9 ± 6.9
ASA-PS	3 [2, 4]
Adult patients	65 (87.8)
Age at first surgery (years)	55.4 [20.0, 86.1]
Pediatric patients	9 (12.2)
Age at first surgery (years)	7.2 [0.7, 13.9]
Range at first surgery (years)	0.7–13.9
Curacao score	
Definite HHT (Curacao score > 2)	59 (79.7)
Suspected HHT (Curacao score = 2)	15 (20.3)
Spontaneous and recurrent epistaxis	67
Multiple mucocutaneous telangiectasias	60
Visceral involvement	67
First-degree relative with HHT	47
Cardiovascular disease	28 (37.8)[a]
Coronary artery disease	7
Heart failure	17
Left ventricular failure	3
Right ventricular failure	3
High-output failure	11
Valvular disease	4
Atrial fibrillation	12[c]
Pulmonary disease	51 (68.9)[a]
Arteriovenous malformation	42
Pulmonary hypertension	11
Home oxygen	2
Pulmonary embolism history	7
Moderate–severe COPD	6
Home oxygen	2
Neurological disease	16 (21.6)[a]
Arteriovenous malformation	7[b]
Brain abscess	1
Cerebral hemorrhage	2
Stroke or transient ischemic attack	7
Seizure disorder	2
Encephalopathy	1
Hepatic disease	29 (39.2)[a]
Arteriovenous malformation	25
Cirrhosis/portal hypertension	4
Gastrointestinal bleed	25 (33.8)
Iron deficiency anemia	48 (64.7)
End-stage kidney disease	2 (2.7)

Data presented at number of patients (percentage), mean ± standard deviation for continuous variables, or median [range] [interquartile range] for nonparametric variables

HHT hereditary hemorrhagic telangiectasia, *ASA-PS* American Society of Anesthesiologists physical status, *COPD* chronic obstructive lung disease

[a] Patients may have multiple conditions per organ system class

[b] Seven patients had arteriovenous malformations of the brain and one also of the thoracic spine

[c] Atrial fibrillation was only found in adult patients, of which 5 had congestive heart failure, 4 valvular disease, 3 pulmonary hypertension, and 10 iron deficiency anemia

disorder typically appear during adolescence, with the most common manifestation being epistaxis. Gastrointestinal bleeding may occur later in life. Larger AVMs in the lung, liver, or brain can result in sudden and potentially catastrophic bleeding or embolic complications. Even though HHT can present challenges to the anesthesia provider, to date only a few descriptions of the anesthetic management of these patients have been published [12–22]. Although larger case series describing obstetrical management of parturients with HHT have been reported; [23, 24] this

Table 2 Surgical and anesthetic characteristics of patients with hereditary hemorrhagic telangiectasia undergoing general anesthesia

	Surgeries ($n = 163$)
Procedural category	
Otolaryngology procedure	87 (53.4)
Cauterization for epistaxis	50
Septodermoplasty	21
Other procedures for telangiectasias	6
Unrelated procedures	10
Interventional radiology procedure	10 (6.1)
Pulmonary arteriovenous malformation coil	7
Central nervous system arteriovenous malformation coil	2
Inferior vena cava filter placement	1
General surgery	27 (16.6)
Intraperitoneal	19
Laparoscopic	13
Diagnostic procedures	13 (8.0)
Thoracic surgery	7 (4.3)
Cardiac surgery	6 (3.7)
Orthopedic surgery	6 (3.7)
Liver transplant surgery	4 (2.5)
Neurosurgery	2 (1.2)
Urology surgery	1 (0.6)
Emergent surgery	11 (6.7)
Duration of surgery (min)	228 ± 84
Airway management	
Endotracheal tube	160 (98.2)
Fiberoptic/videolaryngoscope	2 (1.2)
Laryngeal mask airway	3 (1.8)
Airway trauma	0
Neuraxial anesthesia	5 (3.1)
Intraoperative blood transfusions	25 (15.3)
Intensive care unit admission	26 (16.0)

Data presented at number of patients (percentage) or mean ± standard deviation

Table 3 Notable therapeutic intervention and complications of patients with hereditary hemorrhagic telangiectasia undergoing general anesthesia

Perioperative blood transfusions	
Procedures for epistaxis	• Septodermoplasty (7)
	• Nasal cauterization (3)
	• Miscellaneous procedures to nasal mucosa (2)
Other procedures	• Cardiac (5)
	• Liver transplant (2)
	• Major general surgeries (3)
	• Orthopedic surgery for septic arthritis (3)
Intensive care unit admission	
Procedures for epistaxis	• Septodermoplasty in a patient with severe pulmonary hypertension for observation (2)
	• Septodermoplasty in a patient with severe pulmonary hypertension and 1-l blood loss
	• Nasal cauterization in a patient with severe pulmonary hypertension and hypoxic respiratory failure from right middle and lower lobe consolidation.
Other procedures	• Cardiac (6)
	• Liver transplant (4)
	• Major general surgeries (5)
	• Thoracic (2)
	• Interventional radiology (3)
	• Tracheostomy (1)
	• Neurosurgical (1)
Postoperative complications	
Epistasis following nonnasal procedures	• Epistaxis noted postoperative day 6 following general surgery. Required transfusion of 11 units of packed red cells and coiling of a nasal arteriovenous malformation
	• Epistaxis noted postoperative day 6 following mitral valve repair. Treated with pressure and topical phenylephrine
Neurological deficits	• Self-limited expressive aphasia manifested 3 days after coiling of complex left cortical pial arteriovenous fistula
	• A coil deployed to a pulmonary arteriovenous malformation migrated to the main middle cerebral artery. It was immediately retrieved by a snare and the patient treated with heparin and tissue plasminogen activator. Complicated by transient hemiparesis
Other	• Pulmonary infarction secondary to coiling of pulmonary arteriovenous malformation

cohort represents the first large series of patients with HHT undergoing general anesthesia.

An important observation from this cohort is that more than 50 % of our patients had documented pulmonary AVMs, a proportion consistent with the reported incidence of these malformations in the general HHT population [2]. In fact,it has been reported that up to 35 % of patients with HTT have pulmonary AVM, and that 50–85 % of those with diagnosed pulmonary AVM have HHT [25]. However, the rate of pulmonary AVMs may be underrepresented, because many patients can be asymptomatic and are therefore not evaluated. These AVMs allow for paradoxical shunting of emboli from the venous circulation to the arterial circulation, and ischemic strokes or brain abscesses are not uncommon during the lifetime of patients, even in those who have no clinical evidence of

pulmonary AVMs [26]. In our cohort a patient required surgery for a brain abscess and several patients had a history of ischemic strokes. A very unusual complication was encountered in one of our patients during therapeutic intervention to coil his pulmonary AVM: a coil deployed to a pulmonary AVM migrated through the AVM to the cerebral vasculature. Fortunately, none of our other patients experienced a perioperative embolic neurological complications, but such complications in obstetrical care and during dental procedures have been reported [24, 27]. Three of our four patients with valvular disease had a history of endocarditis. Thus, it would be prudent to have a high level of suspicion of pulmonary AVMs in all patients with HHT and appreciate the risk for paradoxical embolism and infectious complications. When caring for HTT patients, great care should be exercised to avoid injecting even a minuscule air bubble with intravenous medications, and drug syringe stopcocks and all other air-trapping components of intravenous tubing should be cleared before use. Precautionary steps to reduce paradoxical embolic complication risk, such as using air filters on intravenous lines and use of appropriate antibiotic prophylaxis, should always be considered [26, 28]. Other consequences of right-to-left shunt from pulmonary AVMs include chronic hypoxia and pulmonary hypertension, as was present in several patients in this cohort. Although review of our records did not reveal overt evidence of problems with oxygenation during surgery from intrapulmonary shunt, this complication is difficult to elicit from a retrospective series. Atrial fibrillation was present frequently in the adult patients. Although the exact mechanism for the development of atrial fibrillation is unclear, most patients had severe cardiopulmonary disease secondary to HHT, which could have contributed to its development.

Large AVMs can affect any other organ system, but typically also involve the liver and central nervous system. Liver involvement was common in our cohort, and four patients underwent liver transplantation for hepatic failure secondary to HHT. Central nervous system AVMs were less frequent, and only 1 patient had a documented spinal AVM. A review of 312 patients with HHT from our center found that that less than 3 % suffered neurological complications from a cerebral AVM, and that most neurological events were secondary to pulmonary AVMs [29]. Spinal AVMs appear to be less frequent; however, a large proportion of pediatric patients with spinal AVMs are subsequently diagnosed with HHT [30]. Most, but not all, spinal AVMs involve the cervical or thoracic spine [30]. Signs and symptoms from spinal AVMs may develop slowly as progressive neurological deficits secondary to compression of neural tissues [30], but these can also present as an acute neurological deficit in the case of rupture [31, 32]. The use of neuraxial anesthesia for labor and delivery has been described [23], and in our series 5 cases had a neuraxial technique in addition to a general anesthetic for postoperative analgesia. Devastating complications of neuraxial anesthesia in patients with spinal AVMs have been reported. For example, spinal AVMs could bleed from direct needle trauma [33]. Also, there is a report of a parturient who developed progressive neurological deficits in the setting of a cervical spinal AVM over several weeks following vaginal delivery with the use of a lumbar labor epidural [34]. Theoretically, the volume from an epidural injectate or a drop in cerebral spinal fluid pressure from dural puncture could place strain on the thin membrane of a spinal AVM, leading to rupture and bleeding, even if the AVM was distal to the needle insertion site [23]. Another consideration that must be made with the use of regional techniques is that a sympathectomy could worsen right-to-left shunt by decreasing systemic arterial resistance without decreasing pulmonary arterial pressure [23]. Thus, the benefits of neuraxial anesthesia have to be carefully considered in patients with HHT for the potential of spinal AVMs.

The most frequently performed procedures in this cohort were nasal surgeries directed at treating recurrent epistaxis. The telangiectasias are thin-walled vascular malformations that can easily bleed following trauma. Lesions on the skin are protected by squamous epithelium and are less likely to hemorrhage, but those present on mucosal surfaces are not similarly protected and can rupture following even minor trauma [35]. Because HHT is a progressive disorder, the frequency of bleeding can increase with age, with the onset of epistaxis during adolescence or young adulthood and development of gastrointestinal bleeding later in life. Repeated episodes of bleeding can result in chronic iron deficiency anemia, as present in the majority of our patients. As a consequence, patients may receive frequent blood transfusions over their lives, as evidenced by 5 of our patients having been found to have antibodies complicating cross-matching for blood transfusions. A surprising observation was that 12 of 25 perioperative blood transfusions were administered to patients having these procedures, including 2 patients who each received blood transfusions for four different procedures. The proclivity of these lesions to bleed is highlighted by 1 patient who developed epistaxis 6 days following an abdominal surgical procedure and required 11 U packed red blood cells before successful embolization of a nasal mucosal AVM. Because even minor trauma to nasal mucosal telangiectasias can induce severe hemorrhage, it is prudent to carefully weigh the risk–benefit ratio of cannulating the nares of HHT patients with nasogastric tubes, temperature probes, or other devices. Another surprising observation is that four of these patients required postoperative management in the intensive care unit. Later in life telangiectasias

also involve the mucosa of the gastrointestinal tract and can lead to bleeding complications. These lesions can involve the oral cavity, which in theory could be traumatized by airway management. Fortunately, none of our patients experienced this complication.

In conclusion, surgical patients with HHT often present with multiorgan involvement from their disease, which can be severe. The anesthesia provider needs to be aware of the high prevalence of pulmonary AVMs, which may be asymptomatic but that can lead to complications from emboli or introduction of infectious material to the systemic circulation. Even in asymptomatic patients, steps should be taken to reduce the risk of paradoxical embolic complications, such as air filters on intravenous lines and appropriate antibiotic prophylaxis. Further AVMs can lead to other complications such as liver failure, cardiac failure, and pulmonary hypertension; therefore, preoperative evaluation should consider the possibility of these HHT-associated comorbid conditions. Spinal involvement with AVM, although rare, could add considerable risk to neuraxial techniques. Hemorrhage from epistaxis can be severe, and relatively focal procedures to the nasal mucosa to control bleeding can require blood transfusions and intensive care unit admissions. Therefore, instrumentation of the nasal mucosa (such as placement of a nasogastric tube) should be performed under extreme caution.

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Conflict of interest Toby N. Weingarten, M.D., Jeffrey W. Hanson, Kissinger O. Anusionwu, Mandi L. Moncrief, Todd J. Opdahl, Danelle D. Schneider, and Juraj Sprung, M.D., declare they have no conflict of interest.

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