Emergencies in hereditary haemorrhagic telangiectasia

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Summary

Background: Hereditary haemorrhagic telangiectasia (HHT) is a systemic autosomal dominant vascular disease. Although the clinical picture is that of a chronic disabling disease, vascular malformations can suddenly lead to life-threatening conditions.

Aim: To assess the frequency and type of emergency acute complications in HHT.

Design: Retrospective case-note review.

Methods: From August 2000 to December 2004, our specialized HHT centre saw 139 patients (74 males, 65 females, mean age 45.5 years, range 14–77) with a definite diagnosis of HHT. We reviewed their clinical files and recorded all visits for acute complications (massive nosebleeds, haematemesis, melaena, haematochezia, haemothorax, haemoptysis, TIA/ischaemic stroke, haemorrhagic stroke, brain abscess).

Results: Fifty patients (35.9%) had at least one acute complication. There were a total of 93 visits potentially involving the emergency department. Most commonly, patients sought urgent medical attention for nosebleeds and gastrointestinal bleeding (63.4%), but there were also disorders of the brain, lung, heart and liver.

Discussion: Acute complications of HHT are not uncommon and can be severe and wide-ranging. Physicians should be aware of HHT and its major complications, as a prompt diagnosis is essential to direct patients to the most appropriate therapies, and to suggest screening for visceral involvement in their relatives.

Introduction

Hereditary Haemorrhagic Telangiectasia (HHT), also known as Rendu-Osler-Weber disease, is an autosomal dominant vascular disease.¹ The vascular malformations are arteriovenous shunts termed telangiectases (if small), or arteriovenous malformations (if large). Clinical manifestations depend on the organ involved. Four diagnostic criteria for HHT have been established:² (i) epistaxis; (ii) telangiectases on the face, fingertips, nasal and oral mucosa; (iii) a family history of HHT; (iv) visceral lesions including gastrointestinal telangiectases, 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.

HHT is a chronic and socially disabling disease, but emergencies may also happen in this setting. Although individual emergency conditions have been previously described in the medical literature, we believe this is the first paper to give an overview of the acute complications of HHT, and to analyse their frequencies and types.

Methods
Clinical files of 139 patients (74 males, 65 females, mean age 45.5 years, range 14–77) with a definite diagnosis of HHT according to the established diagnostic criteria were reviewed to identify patients with acute complications of the disease. All patients were seen at the HHT Centre of the University of Bari, from August 2000 to December 2004; the majority were hospitalized to screen the visceral involvement of the disease while others were treated for acute disease complications. Screening for brain involvement was done using cerebral magnetic resonance imaging and angio-resonance, to detect both cerebral arteriovenous malformations (CAVMs) and ischaemic lesions. Lung involvement due to the presence of pulmonary arteriovenous malformations (PAVMs) was evaluated by contrast echocardiography and lung computed tomography. Liver involvement was studied with computed tomography evidencing intrahepatic shunts, vascular lesions and intraparenchymal telangiectases. A prolonged enhancement of the portal vein during the early arterial phase was considered a sign of hepatic artery/portal vein shunts (arterioportal shunt); opacification of the hepatic veins during the early arterial phase indicated the presence of hepatic artery/hepatic vein shunts (arteriosystemic venous shunt). Evidence of dilated portal veins communicating with the large systemic or hepatic vein during the portal venous phase was considered a sign of intrahepatic communication between the portal/hepatic veins (portosystemic venous shunt). Upper endoscopy, colonoscopy and video-capsule endoscopy were used in some patients to screen for gastrointestinal involvement. All patients gave written informed consent for our use of their data.

The occurrence of major complications (massive nosebleeds, haematemesis and/or melaena or haematochezia, haemotherax, haemoptysis, TIA/ischaemic stroke, haemorrhagic stroke, brain abscess) requiring urgent medical attention was recorded, and their frequencies and types were analysed.

Table 1 Clinical features

<table>
<thead>
<tr>
<th>HHT involvement</th>
<th>Number screened</th>
<th>Positives (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Family history</td>
<td>139</td>
<td>126 (90.6)</td>
</tr>
<tr>
<td>Telangiectases</td>
<td>139</td>
<td>121 (87)</td>
</tr>
<tr>
<td>Nosebleeds</td>
<td>139</td>
<td>123 (88.4)</td>
</tr>
<tr>
<td>CAVMs</td>
<td>96</td>
<td>9 (9.4)</td>
</tr>
<tr>
<td>PAVMs</td>
<td>132</td>
<td>80 (60.6)</td>
</tr>
<tr>
<td>HAVMs</td>
<td>130</td>
<td>87 (66.9)</td>
</tr>
<tr>
<td>Gastrointestinal telangiectases</td>
<td>71</td>
<td>40 (56.3)</td>
</tr>
</tbody>
</table>

CAVMs, cerebral arteriovenous malformations; PAVMS, pulmonary arteriovenous malformations; HAVMs, hepatic arteriovenous malformations.

Results
Of 139 patients with a definite diagnosis of HHT, 50 (35.9%) had at least one acute complication of the disease during their lifetime. These 50 made a total of 93 visits potentially involving the emergency departments: nosebleeds, 34 (36.5%); gastrointestinal tract emergencies, 25 (26.9%); symptoms related to cerebral arteriovenous malformations, 2 (2.1%); TIA/stroke, 7 (7.5%); brain abscesses, 11 (11.8%); lung haemorrhages, 5 (1 haemothorax, 4 haemoptysis) (5.4%); heart emergencies, four (4.3%); liver emergencies, 2 (1%); and miscellaneous, 3 (3.2%) (Table 1).

Nosebleeds were the commonest acute complication of HHT (Table 2). Although haemorrhagic shock was recorded only in two cases, a blood transfusion was required in nine. An asystolic cardiorespiratory arrest occurred after a massive nosebleed with haemorrhagic shock in one patient.

Neurological emergencies affected 17 patients (21.5% of all recorded emergencies), and were due to PAVMs in 15 (88.2%) (see Figure 1) and to CAVMs in the remaining two. Cerebral vascular malformations were found in 15/96 patients screened: four had a venous angioma, one had a cavernous angioma, one had a telangiectasia, and nine had CAVMs (9.4%). An example is shown in Figure 2. Of the nine with CAVMs, four had multiple CAVMs; two of these four were symptomatic, one with seizures and one who died of a cerebral haemorrhage (autopsy not performed). Of 132 patients screened with contrast echocardiography and/or computed tomography, 89 (60.6%) had PAVMs. Eighteen of these 89 (22.5%) had neurological sequelae: nine had ischaemic lesions on cerebral screening, seven had a
brain abscess, and two patients had both ischaemic lesions and a brain abscess. Globally, ischaemic cerebral lesions were found in 15 patients, of whom 11 had concomitant PAVMs (conversely, 13.7% of patients with PAVMs suffered from cerebral ischemia) and of these, six had symptomatic stroke (one also had a TIA). Five patients had concomitant diseases together with PAVMs potentially accounting for cerebral ischaemia. Table 3 summarizes features of patients with cerebral ischaemia. With regard to brain abscess, this complication has previously been reported in 6.6% of the global HHT population and in 9/80 patients with PAVMs (11.25%). The clinical features of six of the nine patients in the present series have been previously described.3

Lung emergencies (haemothorax, haemoptysis) occurred in three patients: one patient had an episode of haemothorax because of a bleeding PAVM while the other two presented episodes of haemoptysis and had PAVMs but also bronchial telangiectases (with bronchoscopy). However, haemoptysis was never massive, and emergency treatment (intubation, embolotherapy) was never required.

### Table 2  Acute complications of HHT

<table>
<thead>
<tr>
<th>Complication</th>
<th>Episodes</th>
<th>Patients</th>
<th>Mean age (range) (years)</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nosebleeds</td>
<td>34 (36.5%)</td>
<td>22 (44%)</td>
<td>40.8 (19–69)</td>
<td>1 seizure; 1 likely brain haemorrhage</td>
</tr>
<tr>
<td>CAVMs</td>
<td>2 (2.1%)</td>
<td>2 (4%)</td>
<td>57.5 (46–69)</td>
<td></td>
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<tr>
<td>TIA/stroke</td>
<td>7 (7.5%)</td>
<td>6 (12%)</td>
<td>44.8 (14–61)</td>
<td></td>
</tr>
<tr>
<td>Brain abscess</td>
<td>11 (11.8%)</td>
<td>9 (18%)</td>
<td>31.6 (19–45)</td>
<td></td>
</tr>
<tr>
<td>Lung haemorrhages</td>
<td>5 (5.4%)</td>
<td>3 (6%)</td>
<td>Haemothorax 55; haemoptysis 25.5 (25–26)</td>
<td></td>
</tr>
<tr>
<td>Heart</td>
<td>4 (4.3%)</td>
<td>3 (6%)</td>
<td>Angina pectoris 59; heart failure 67 (59–73)</td>
<td></td>
</tr>
<tr>
<td>Liver</td>
<td>2 (2.1%)</td>
<td>2 (4%)</td>
<td>41 (33–49)</td>
<td>2 severe biliary disease</td>
</tr>
<tr>
<td>Gastrointestinal tract</td>
<td>25 (26.9%)</td>
<td>18 (36%)</td>
<td>Melaena 52.8 (25–72); haematochezia 45 (29–60)</td>
<td>21 haematemesis and/or melaena; 4 haematochezia</td>
</tr>
<tr>
<td>Miscellaneous</td>
<td>3 (3.2%)</td>
<td>3 (6%)</td>
<td>46 (31–67)</td>
<td>1 bleeding from a lingual telangiectasia; 1 bleeding from a labial telangiectasia; 1 splenic infarction</td>
</tr>
<tr>
<td>Total</td>
<td>93</td>
<td>50</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

CAVMs, cerebral arteriovenous malformations; TIA, transient ischaemic attack.

**Figure 1.** Selective pulmonary angiogram revealing arteriovenous malformation in the pulmonary circulation of a patient with hereditary haemorrhagic telangiectasia, with the courtesy of Dr M. Memeo.

**Figure 2.** Angiogram of cerebral circulation showing a large parieto-occipital arteriovenous malformation in a patient with hereditary haemorrhagic telangiectasia.
Three patients had cardiac emergencies. One patient with no history of coronary artery disease had an episode of angina pectoris on the fourth day after embolotherapy, as demonstrated by ST segment alterations on ECG. Episodes of heart failure were noted in the other two patients, and CT scans detected arterioporal and arteriosystemic shunting, respectively, while no other medical condition potentially associated with heart failure (e.g. arterial hypertension, ischaemic heart disease) was present.

HHT liver involvement (Figure 3) was considered responsible for portal hypertension in six patients (one with concomitant HCV infection, two with previous HBV infections), but no emergency related to portal hypertension was recorded. Two patients reported severe episodes of biliary disease due to HHT, and underwent orthotopic liver transplantation because of biliary sepsis.4

Gastrointestinal bleeding occurred in 18 subjects, 14 of whom presented with haematemeses and/or melaena requiring transfusions, including one who died during hospitalization. Upper endoscopy was performed in 12/14 patients revealing gastrointestinal telangiectases in 11 (concomitant gastritis, gastric ulcer and duodenal ulcer were noted in one patient each) and gastritis alone in one patient. Haematochezia was observed in 4/18 subjects; colonoscopy was performed in two, demonstrating polyposis in one while the other was normal; one of the remaining two patients without colonoscopy had haemorrhoids on inspection.

Two patients visited the emergency department because of bleeding from lingual and labial telangiectases, respectively. Computed tomography showed a splenic infarction and a calcific splenic artery in another patient, who had also PAVMs. Although not included in our series, one patient treated with oestrogen therapy for nosebleeds died because of massive pulmonary embolism. Another three patients, not treated with pro-thrombotic drugs, demonstrated deep-vein thromboses, and pulmonary embolism was also noted in one. All of these four patients had PAVMs and a high risk of systemic embolism.

**Discussion**

More than one-third of patients in our series (35.9%) sought urgent medical attention for HHT-related
conditions. Although nosebleeds (36.5%) and gastrointestinal bleeding (26.9%) accounted for two-thirds of emergency situations, acute complications due to brain, lung, heart and liver involvement were also recorded. Unfortunately, we could not evaluate the mortality due to such events, because of patient survivor bias, but clearly, life-threatening illnesses are not uncommon among HHT patients. In another study, we also observed that mortality shows a double peak: an early peak for the <50 years age group and a late peak for the 60–79 year age group (unpublished data). Although mortality was not analysed with regard to the cause of death, the peak in younger patients could be due to major acute complications of the disease. Similarly, an excess mortality in patients aged <60 years has been observed by other authors.5

Although HHT is basically an haemorrhagic disease, thromboembolic complications are not uncommon (11 patients with ischaemic lesions, one patient with angina, one patient with splenic infarction). If all thromboembolic episodes are taken into account, these figures are even more relevant: four patients had ischaemic lesions without evidence of PAVMs, and four patients had a deep-vein thrombosis (with pulmonary thromboembolism in two). It is evident that patients with HHT cannot be excluded from classic cardiovascular and thromboembolic risk factors; moreover, PAVMs and the use of pro-thrombotic drugs both increase the risks. This is an important issue both for therapy (use of anti-aggregants/anti-coagulants for thromboembolic manifestations in haemorrhagic disease) and prevention (e.g. use of aspirin in the setting of cardiovascular risk). Lastly, the major complications of HHT can be avoided by means of adequate screening and treatment protocols; we specifically investigated this issue in the setting of brain abscess, emphasizing that medical inaccuracies may play a role in the development of such complication.3

Individual organ involvement is discussed below.

Nosebleeds affect almost 90% of HHT patients6 and are the most common cause of emergency visits. The pattern of bleeding can range from mild daily bleeding to sporadic and severe episodes, but bleeding is occasionally the cause of a haemorrhagic shock. This occurred on only two occasions in our series (one complicated by cardiac arrest). Nasal packing should be avoided if possible, but patients can be taught to pack their nose themselves for uncontrollable nosebleeds, using smooth packings with latex, polyurethane or carboxymethyl-cellulose to make the removal of packing safer. The embolization of external carotid artery branches can provide relief for acute relief of symptoms, but it is ineffective for long-term management as collateral arteries develop.7

In HHT, arteriovenous malformations can be located in the brain (CAVMs); moreover cerebral ischemia and brain abscess may occur as complications of PAVMs. In a series of 321 patients, Maher et al.8 observed nine patients (2.8%) with symptomatic cerebral vascular malformations and 26 patients (8.1%) with symptomatic PAVMs. In our series, we found that 17 patients had neurological complications of HHT (21.5% of all recorded emergencies), which in most cases were due to PAVMs (88.2%). The reason for the increased prevalence of PAVM-related neurological complications in our patients is unclear, but it is probably due both to a greater prevalence of PAVMs in our general population (60.6%), and a lower prevalence of CAVMs (9.4%).

Although the association between PAVMs and brain ischaemia has been clearly demonstrated,9 it can be difficult to establish the role of PAVMs in single patients, as concomitant disease is often present (Table 3). Other cerebrovascular risk factors can affect HHT patients, as in the general population. We found four patients with ischaemic lesions without PAVMs; this is noteworthy because anti-aggregant therapy should not be administered to these patients, as it can worsen nosebleeds. In fact, we observed ischaemic lesions in a patient who had recently discontinued aspirin because of worsening nosebleeds.

Brain abscess in the setting of a right to left shunt (PAVMs or cyanotic heart diseases) is considered secondary to paradoxical embolization.10 In fact, a septic embolus can produce an actual ischaemic stroke, creating a nidus for bacterial infection, or infarction can be due to a sterile embolus, with subsequent bacterial seeding of the infarcted area. In some patients, polycythaemia can be responsible for cerebral infarction. Although (due to the hemorrhagic nature of the disease) this is quite rare in HHT, higher levels of haemoglobin are associated with an increased risk of developing brain abscess in patients with PAVMs and HHT.3 About 10% of HHT patients can be expected to develop a brain abscess over their lifetime;11 conversely, we found that at least 2/126 cases of brain abscess were due to HHT.12 As the mean age of patients with brain abscesses and PAVMs (29.2 years in our case series and 40.8 in other series11) is younger than that of brain abscess patients in the general population, the recalculated prevalence of HHT among patients younger than 50 years increases to 2/75 (2.7%).

As regards lung involvement, the majority of PAVMs are asymptomatic.13 14 Lung gas-exchange function is affected, leading to various degrees of
hypoxaemia according to the number and size of vascular malformations. Chronic dyspnoea in HHT patients can be exacerbated by pneumonia or cardiogenic pulmonary oedema. Bleeding from a PAVM can lead to an emergency scenario: a PAVM can haemorrhage into a bronchus or into the pleural cavity determining haemoptysis and haemothorax, respectively. The prevalence of haemoptysis in these patients ranges from 6% to 13%,\textsuperscript{15–17} differences can be related to the screened population (symptomatic patients or all patients) or to the referral centre (specialized centre or general hospital). Haemoptysis is rarely due to bleeding bronchial telangiectases.\textsuperscript{18} In our series, episodes of haemoptysis occurred in two patients with bronchial telangiectases in addition to PAVMs. Prevalence of haemothorax is lower than haemoptysis (4–9%)\textsuperscript{14,19} and was described in one patient.

The heart is rarely affected by HHT. The most common condition is high-output cardiac failure due to arteriovenous shunting in the liver.\textsuperscript{20} Episodes of major bleeding or other conditions, such as arrhythmias, fever, and excessive salt intake, can cause a worsening of symptoms. Occasionally, angina can be due to paradoxical embolism through a PAVM or as a result of coronary arteriovenous fistulas.\textsuperscript{21} Cardiac tamponade from pericardial vascular dysplasia has also been described.\textsuperscript{22} In our case series, we recorded an angina episode in the fourth day after embolotherapy, and episodes of heart failure in two patients with HHT liver involvement (arterioportal shunting in one and arteriosystemic shunting in the other).

Symptomatic liver involvement occurs in 8–31% of patients,\textsuperscript{23–25} but hepatic vascular malformations have been demonstrated in a higher percentage of patients.\textsuperscript{26,27} Clinical manifestations of liver involvement are related to three types of shunting\textsuperscript{20} and their effect on the liver parenchyma: high-output heart failure is the consequence of arteriovenous shunting; portal hypertension is related to arterioportal shunt or to a nodular transformation of the liver (pseudocirrhosis) induced by abnormal hepatic blood flow; biliary disease could be related to ischaemia of biliary ducts; portosystemic encephalopathy is related to intrahepatic portosystemic shunting or can be the consequence of portal hypertension; abdominal angina is the consequence of a mesenteric vascular steal through the pancreatic–duodenal arteries. Cardiogenic pulmonary oedema in the setting of high-output heart failure has already been described (see paragraph above). In our series, we found no acute complications deriving from portal hypertension, although such conditions were present in six patients: two had severe biliary disease (biliary sepsis) and eventually required orthotopic liver transplantation.

Although nosebleeds are usually the main source of bleeding in HHT patients, gastrointestinal haemorrhage is a frequent issue, affecting 13–33% of patients.\textsuperscript{28,29} It can be difficult to distinguish digestive bleeding from swallowed blood due to epistaxis; as the entire gastrointestinal tract is involved, localization of the precise bleeding site can also be difficult.\textsuperscript{30} Bleeding is more commonly a chronic dripping, clinically evident as anaemia, and cannot be considered epistaxis, although haematemesis, melaena and haematochezia are not uncommon. Episodes of major bleeding were found in 18/139 patients of our series; as observed in other series,\textsuperscript{31} concomitant disease has to be taken into account when gastrointestinal bleeding occurs.

The involvement of other organs can sometimes result in acute complications. Sudden visual loss has been described because of ocular involvement\textsuperscript{32} or as a consequence of paradoxical embolization.\textsuperscript{33} Bleeding from kidney and urinary vascular malformations is another rare complication.\textsuperscript{34–36} Although uterine bleeding has been described because of uterine telangiectases, this condition is more commonly an adverse effect of oestrogen therapy, used to control epistaxis or gastrointestinal bleeding.\textsuperscript{37,38}

Conclusions

The concomitance of thromboembolic disease or common cardiovascular risk factors in the setting of a haemorrhagic disease is especially challenging for physicians. The clinical picture of HHT is frequently that of a chronic disease, with daily nosebleeds affecting the quality of life of patients,\textsuperscript{39} but patients may harbour vascular malformations that can suddenly give rise to life-threatening conditions. Physicians should be aware of such conditions, and maintain a high suspicion index for patients with HHT in an emergency setting. Identification of the correct pathogenesis is crucial for treatment to avoid relapse or further complications of the disease, both in patients and their relatives.

Acknowledgements

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References


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