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Clinical Manifestations of Hereditary Hemorrhagic Telangiectasia

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Sixty-four patients with symptomatic hereditary hemorrhagic telangiectasia were retrospectively studied in order to determine the true incidence of clinical manifestations in this disease. This select group had a significantly higher incidence of gastrointestinal hemorrhage and pulmonary arterovenous fistula formation than has been previously reported. Data are presented regarding the course and severity of nasal and gastrointestinal hemorrhage, the use of endoscopy for diagnosis, the incidence of associated neurological, cardiac, and hepatic disease, and mortality.

INTRODUCTION

Hereditary hemorrhagic telangiectasia (HHT) is an autosomal dominant inherited disease (1) characterized by telangiectasias of the skin, mucous membranes, and various organ systems. Its clinical presentation is variable as regards both number of vascular lesions and severity of organ dysfunction secondary to these lesions. Telangiectasias have been described on all body surfaces, but are most common about the head, the extremities, and the chest (2). They also occur in all parts of the alimentary tract (3), as well as the lungs (4), brain (2), retina (5), and liver (6, 7).

Previous studies attempting to define the clinical manifestations of this disease included asymptomatic relatives of index cases (2, 4), thereby underestimating the incidence and severity of organ specific lesions. This study was undertaken to define the manifestations of HHT in a symptomatic patient population to establish a more accurate estimate of the incidence and severity of these findings. This is the subset of patients that the clinician is likely to see.

METHODS

The records of all patients seen at the University of Michigan affiliated hospitals and clinics (University Hospital 1954–1980, Ann Arbor VA Hospital 1965–1980, and Wayne County General Hospital 1970–1980) with the diagnosis of HHT were reviewed. Sixty four patients fulfilled the following requirements: *1*) cutaneous and mucosal telangiectasias, *2*) active HHT related disease at the time of presentation, and *3*) a family history and/or personal history of episodic undiagnosed nasal or gastrointestinal hemorrhage.

RESULTS

Fifty-six percent of the patients were male and 44% were female. There was no relationship of sex to severity of illness or number of organ systems involved. The age at diagnosis varied from 2 days to 85 years with a median age of 44 years. Symptoms began at a median of 20 years before diagnosis (range 0–78 years). A family history compatible with the diagnosis of HHT was recorded in 74%.

Clinical manifestations (incidence)

Table 1 lists the various clinical manifestations of patients at inital presentation. The most common sign was epistaxis with 78% of patients having this at some time during their course, and 51% of patients having this sign at initial presentation. Gastrointestinal (GI) bleeding was second in overall frequency at 44%, and this was the initial sign in 25%. The remaining patients had a wide range of complaints related to skin and pulmonary lesions as well as CNS disease. Three patients who presented with complaints unrelated to HHT were found to have HHT-related disease.

TABLE 1
HHT: Presenting Manifestations (64 Patients)

	n	%
Epistaxis	33	51
GI bleeding	16	25
Abnormal chest x-ray	3	5
Headache (brain abscess)	2	3
Seizure (CNS emboli)	2	3
Progressive skin lesions	2	3
Cyanosis (large pulmonary arteriovenous malformation with emboli)	1	<2
Transient ischemic attacks	1	<2
Abdominal pain, pulsatile right upper quadrant		
Mass (hepatic AVM)	1	<2

Skin and mucosal lesions

Telangiectasias were found most commonly on the hands and feet. The most frequent locations were the palms and soles of the feet, tips of the digits, as well as the subungual and periungual areas (Table 2). Although mucosal telangiectasias were seen at one time or another on the nasal mucosa of 78% of patients, these are of little use diagnostically because of obscuration of the nasal mucosa related to recurrent epistaxis. No correlation between the location of skin or mucosal lesions and GI hemorrhage was found.

Epistaxis

Epistaxis was not only the most common presenting manifestation of HHT but also the most common symptom overall (78%). We divided the group into "minor" and "major" categories depending on the requirement for transfusion (minor = no transfusions, major = greater than or equal to one transfusion). Slightly more than one-third of all patients with epistaxis had major hemorrhage (Table 3). More than one-half developed epistaxis in the first decade of life (Fig. 1). The course of epistaxis was progressive in 54% and static in 42%, the latter defined as no change from the previous pattern of bleeding or transfusion requirements. Four percent had spontaneous regression of bleeding. Ten patients with major epistaxis were treated with varying doses of estrogen, and of the these five had no sustained response while five had significant reduction or cessation of epistaxis for follow-up periods of 2–10 years. All of the estrogen-treated patients had significant unpleasant symptoms related to therapy, primarily gynecomastia, and vaginal bleeding, but none had any recognizable major complications. Fourteen

TABLE 2
HHT: Distribution of telangiectasias (64 Patients)

	n	%
Skin		
Hands/feet	43	67
Face	35	55
Chest	25	39
Mucosa		
Nose	50	78
Lips	45	70
Tongue	40	62
Cheek	34	53
Palate	21	32
Conjunctiva	6	9

TABLE 3
HHT: Epistaxis

	n	%
Incidence	50	78
Minor (no transfusion)	27	42
Major (transfusion)	23	36

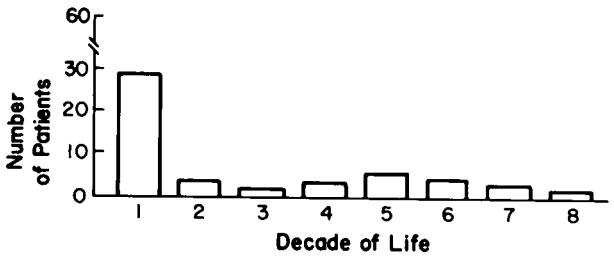

FIG. 1. Epistaxis: age at onset.

patients with major epistaxis underwent a total of 20 septal dermoplasty procedures. Of the 11 patients followed for 2–4 years, 60% had no beneficial effects while 25% had reduction or cessation of bleeding.

GI hemorrhage

GI hemorrhage was the second most common presenting manifestation, and was present at some time in 28 of the 64 patients (44%). Using the same minor/major classification scheme that was applied to epistaxis, a little more than half of the patients had major GI hemorrhage, which represents 25% of the entire series (Table 4). In contrast to epistaxis, the onset of GI bleeding was usually in the fifth decade of life or later (Fig. 2). To describe accurately the site of bleeding, the following criteria were applied: *1*) upper GI bleeding was defined by hematemesis, a positive nasogastric aspirate in the absence of epistaxis, or actively bleeding lesions found at the time of upper GI endoscopy; *2*) lower GI bleeding was defined by hematochezia or actively bleeding lesions at sigmoidoscopy; *3*) if criteria 1 or 2 were not fulfilled, bleeding was considered indeterminate, *e.g.*, melena with a negative endoscopy or endoscopic visualization of nonbleeding telangiectasias. Eleven (40%) of 28 patients met the criteria for upper, three (10%) for lower GI bleeding, and in 14 (50%) the bleeding site was indeterminate. Eighteen of the 28 patients were followed for 2–6 years, and of these two-thirds had continued chronic intermittent bleeding, while one-third had steady progression in the degree of hemorrhage. In contrast to epistaxis, none of the patients with GI hemorrhage underwent spontaneous regression.

Esophagogastroduodenoscopy was performed on 17 patients and 12 (70%) had typical lesions in the stomach, although none was actively bleeding at the time of the examination (Table 5). No esophageal or duodenal lesions were described. Nine percent of all patients and 14% of those with GI hemorrhage had coexisting duodenal ulcer disease. Sigmoidoscopy demonstrated telangiectasias in only four of the 23 patients studied and barium x-rays were uniformly nonrevealing. Angiography demonstrated multiple visceral telangiectasias in two patients where prior evaluation including upper endoscopy was unrewarding. Colonoscopy was performed in one patient and showed an actively bleeding

TABLE 4
HHT: GI Hemorrhage

	n	%
Incidence	28	44
Minor (no transfusion)	12	19
Major (transfusion)	16	25

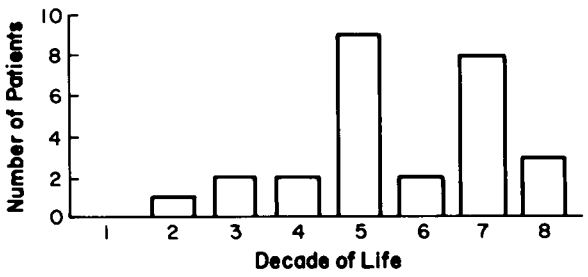

FIG. 2. GI hemorrhage: age at onset.

TABLE 5
HHT: GI Hemorrhage (Diagnostic Methods)

	Done	Positive
Esophagogastroduodenoscopy	17	12
Sigmoidoscopy	22	4
Colonoscopy	1	1
Barium x-rays	56	0
Angiography	2	2

telangiectatic lesion that was successfully treated by electrocautery.

Pulmonary lesions

Twenty percent of our patients had pulmonary arteriovenous fistulas (AVFs) and of these approximately one-third had multiple lung lesions. All were demonstrable on standard chest x-rays (and confirmed angiographically) except in one case where multiple microscopic AVFs were diagnosed at autopsy. Among nine patients with solitary AVFs, one had resultant polycythemia and transient ischemic attacks; otherwise none had symptoms or signs directly referable to their lung lesions. In contrast, all three patients with multiple macroscopic AV fistulas presented with major CNS complications as shown in Table 6. Four of the five patients with CNS complications had pulmonary AVFs, while one patient with a brain abscess had no evidence of pulmonary lesions clinically or at postmortem examination.

Liver disease

Liver disease was defined as the presence of hepatomegaly and/or levels of serum transaminases or alkaline phosphatase more than two times normal. Twenty patients (31%) fulfilled these criteria, and 10 of these either underwent percutaneous liver biopsy or came to postmortem examination. Thirty percent had passive hepatic congestion and 30% had hepatic telangiectasias. Iron overload (3+ or more) was seen in 50%. Periportal fibrosis (eight patients), occasional serate hepatocellular necrosis (three patients), or lobular fat deposition without a significant history of alcohol intake (two patients) were in 40% of patients. There was no patient with fully developed cirrhosis, bridging necrosis, or chronic active hepatitis. Combinations of these findings were found in half of the patients studied.

TABLE 6
HHT: CNS Manifestations

	n	%
Overall incidence	5	8
Transient ischemic attack	2	3
Brain abscess	2	3
Arteriovenous malformation	1	0*
Cerebrovascular accident	1	2

* Included under brain abscess.

Miscellaneous disease

Twenty percent had clinical evidence of right, left, or biventricular cardiac failure without any explanation other than HHT. The patients with pulmonary AVFs were remarkably free of clinically apparent cardiac disease, with high output states due to anemia and systemic arteriovenous shunting accounting for almost all cases of heart disease. No scintigraphic or cardiac angiographic studies were performed. There was no evidence of iron overload clinically or at the time of autopsy.

Only one of the 64 patients had Von Willebrand's disease and she was lost to follow-up at age 20, by which time she had not sustained any life-threatening hemorrhage.

Eleven of the 64 patients died in one of our hospitals, and of these, six died of unrelated causes at a median age of 75 years, while five died of causes directly related to HHT or its therapy at a median age of 46 years.

DISCUSSION

All prior studies of HHT have included families or large groups containing varying numbers of asymptomatic individuals. The data obtained from such studies, although valid as stated, will necessarily underestimate the frequency of the various components of the syndrome depending on the number of asymptomatic persons included. When this number or fraction is not given, the data presented cannot be interpreted in a meaningful way. In addition, our diagnostic criteria were chosen to separate HHT as accurately as possible from the various other diseases with which it may be confused (Table 7), something that has not been adhered to strictly in prior studies.

The equal sex distribution and the high percentage

of positive family histories in this study are in accord with earlier estimates (2, 4). The distribution of skin and mucosal lesions differed from that of Smith *et al.* (2) in that we did not find a correlation between GI bleeding and telangiectatic lesions of the lips. Despite the absence of any specific prognostic significance, the distribution of lesions is of importance in evaluating epistaxis or GI bleeding of unknown etiology.

The incidence for many of the clinical manifestations of this disease has not been previously described, although the prominence of epistaxis and GI hemorrhage is not unexpected. In the only other study of the incidence of GI hemorrhage in HHT (2) only 13% of 159 patients bled from the GI tract. This is in striking contrast to the 44% of 64 patients reported here, and is likely due to the fact that the earlier study included an unspecified number of asymptomatic family members.

The delay in onset of GI hemorrhage in contrast to the early onset of epistaxis deserves further comment. Since degenerative vascular telangiectasias are a common endoscopic finding in the elderly and may be a source of significant GI bleeding (8, 9) perhaps such degenerative changes have an additive effect on the genetic defect in HHT, accounting for the relatively late onset and high incidence of GI bleeding that we observed. The early onset of epistaxis is explainable by the location of the mucosal lesions and their accessibility to trauma (10).

Therapy for hemorrhage in HHT regardless of the source has been disappointing. Transfusion and iron supplementation remain the only well-accepted treatments, with the possible exception of nasal dermoplasty for epistaxis. This operation involves placing a skin graft intranasally to protect the fragile telangiectatic vessels from local trauma. Previous series have shown this procedure to be useful, with success rates much higher than we found (11, 12). Variable factors such as patient selection and surgical skill enter into the decision to proceed with this operation. Medical therapy for epistaxis in HHT has included the administration of such varied substances as ascorbic acid, rutin, snake venon, androgens, and estrogens. None has stood the test of time with the possible exception of estrogen therapy, which seems to be of some benefit in noncontrolled trials (11, 13). Its mechanism of action is believed to be induction of squamous metaplasia of the nasal mucosa, thereby providing a protective barrier for the telangiectasias.

TABLE 7
Vascular Malformations Involving Skin and/or Mucous Membrance

HHT
Multiple phlebectasia
Blue rubber bleb nevus syndrome
Generalized universal telangiectasia
Turner's syndrome
Maffucci's syndrome
Essential telangiectasia
Scleroderma
Senile hemangioma
Simple spider angioma

A review of the literature regarding GI bleeding in HHT indicates that in select cases surgical resection can be effective in treating isolated repeatedly bleeding telangiectasias, at least in the short term (15, 16). These operations have not met with lasting success due to repeated episodes of bleeding from other mucosal lesions, but have been of use in the management of uncontrollable life-threatening hemorrhage. Location of the source of GI bleeding is crucial. Definition of the source of bleeding could only be accomplished in 50% of our patients by clinical means although telangiectasias could be seen at the time of upper GI endoscopy in 70%. The specific role of endoscopic therapy, whether by electrocautery or laser photocoagulation, is poorly defined. A major limiting factor is the difficulty encountered in endoscopic visualization of actively bleeding leisons. Although vascular lesions can be easily visualized, therapy aimed at potential rather than actual bleeding sources may be fruitless and possibly dangerous. Clinical bleeding localized to the upper GI tract was only found in 40% of our patients. The use of colonoscopy to localize potential colonic telangiectasias and ^{99m}Tc red blood cell scan to localize low grade bleeding points may improve localization overall, but the impact of this on therapy remains uncertain.

The incidence of pulmonary AVFs has been estimated at 6–7% based on family studies (4, 17) of HHT but this lesion was far more common (20%) in this select population. Secondary CNS disease may be due to a variety of mechanisms including hypoxemia, polycythemia, and embolization. Separation of infected thrombi from the wall of the AVF is thought to be responsible for brain abscess formation. In this study, solitary AVFs did not predispose to a high risk of CNS disease, whereas multiple AVFs universally did. The occurrence of a brain abscess without pulmonary AVFs is interesting; the proposed mechanism is that oral flora gained direct access to the intracranial venous system through mucosal telangiectasias.

The pathological changes in the liver in HHT have been described (6, 7, 18). The degree of hepatic dysfunction may be severe leading to portal hypertension and portosystemic encephalopathy (19, 20). Patients with HHT are at risk for developing liver disease in a variety of ways: *1*) peliosis hepatitis, hepatic adenoma, or even hepatocellular carcinoma secondary to long-term hormonal therapy; *2*) acute hepatitis potentially followed by chronic liver disease and cirrhosis secondary to multiple transfusions; *3*) iron overload state secondary to transfusions and/or chronic oral iron therapy; *4*) passive congestion secondary to high output heart failure caused by chronic anemia and arteriovenous shunting; *5*) direct involvement of the liver with HHT, either in the form of macroscopic AVMs, isolated

microscopic telangiectasias, or a unique form of fibrosis (telangiectasia-associated hepatic fibrosis or "pseudocirrhosis"). Our results show that combinations of these findings are not unusual, with hepatic iron overload being the most common single entity observed (50%). None of the patients studied had cirrhosis or a significant degree of fibrosis, but isolated hepatic telangiectasias were seen in 30%.

The potentially devastating combination of Von Willebrand's disease and HHT has been previously reported (21) but it remains unclear if this is a true association or simply the random occurrrence of two rare diseases in the same patient.

The increased incidence of duodenal ulcer with HHT described by Smith *et al.* (2) was observed among our patients as well, with a 14% incidence of duodenal ulcer in patients who bled from the GI tract and 9% overall. These numbers indicate that patients with HHT have a higher chance of developing duodenal ulcer than the general population, but the pathophysiological link between the two disease processes remains to be established.

CONCLUSION

Patients with HHT presenting for medical attention have a much higher incidence of significant multiorgan system disease than previously reported. Nasal bleeding remains the most common source for morbidity, and currently available therapy (either hormonal or surgical) still results in variable degrees of success.

GI bleeding occurs in 44% of patients but the source of bleeding has been difficult to define despite the use of urgent upper GI endoscopy. The application of endoscopic therapy (electrocoagulation and laser photocoagulation) to visible lesions must be studied in a controlled fashion to determine their use in this disease, where localization of bleeding is difficult and supportive therapy is the only effective form of management.

In addition to the overwhelming incidence of GI hemorrhage in patients with symptomatic HHT, pulmonary disease also appears to be more common than previously described, and leads to a high incidence of devastating CNS manifestations such as brain abscess and cerebrovascular accident. Close attention to these complications must be routinely given during initial examination of the patient with HHT.

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