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REVIEW ARTICLE

A rare and misdiagnosed bleeding disorder: hereditary hemorrhagic telangiectasia

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History of the disease

Hereditary hemorrhagic telangiectasia (HHT) is an autosomal dominant inherited disease in which abnormal communications between arteries and veins, the so-called telangiectases, occur in the skin, mucosal surfaces, and solid organs [1]. Small telangiectases on the face may present an important cosmetic problem, but larger lesions can be a source of chronic blood loss, systemic emboli, hypoxemia, hepatic dysfunction, and high-output cardiac failure. HHT is an uncommon disease with an overall frequency calculated between 1 per 5000 and 10 000 persons [2]. In the literature, over the past 160 years, many disorders have been attributed to HHT but the criteria for a definite diagnosis have been established only few years ago. The clinical diagnosis of HHT is based on the presence of at least three of the following characteristics: recurrent epistaxis, mucocutaneous telangiectases, evidence of autosomal dominant inheritance, and visceral arteriovenous malformations [3].

No mention of illnesses which could be reasonably attributed to HHT or a similar disease can be found in the early medical discourses of Hippocrates, Galenus, Avicenna. Moreover, HHT or recurring nosebleeding are not mentioned in the Bible, nor in the ancient writings from Egypt, Greece and Rome. In 1865, an hereditary form of epistaxis was described for the first time in *The Lancet*; Benjamin Guy Babington, an English physician, published a report on a patient who suffered from nosebleeds since he was 8 years old, as was also his mother [4]. Previously, in 1864, Gawen Sutton had already described the case of a man with vascular malformations and recurrent hemorrhage but since he was an orphan, no information regarding the family was available [5]. The unusual association of multiple telangiectases on mucous membranes and the skin was observed both by John Wickham Legg in 1876 [6] and Henry Louis Marie Rendu in 1896 [7,8]. At the meeting of the Royal Medical and Surgical Society in London, Wickham Legg described a patient with familiar epistaxis and multiple small 'nevi' which developed during his lifetime. In his case report, Henry Rendu described a 52-year-old man with anemia and daily recurrence of nosebleeds since the age of 12 years whose father also had a history of melena; other hemorrhages were not present but Rendu described numerous small red spots on the nose, tongue and upper lips due to dilatation of superficial vessels (telangiectases). In the paper, two additional cases were described in a family in which epistaxis had occurred in seven members; both patients had nosebleeds from childhood together with telangiectases. The condition was not related to hemophilia.

Subsequently, in the John Hopkins Hospital Bulletin in 1901, Sir William Osler, a famous Canadian physician, reported on three families with hereditary telangiectasia and hemorrhages [9]. In the first family, George B., a sailor aged 57, was admitted to the John Hopkins Hospital with weakness, anemia and swelling of the feet. From childhood his father had had bleeding from the nose and cuts. His mother was healthy but two of his four brothers suffered from epistaxis. George had always been very anemic and often bled from an angioma on the lower lip and on the mucosa of the septum. His face, ears, nose, cheeks and lips presented numerous telangiectases. In the second family, William B., aged 55, reported bleeding episodes every day but was admitted to the hospital because of nausea, vomiting and abdominal pain from which he had suffered for several months. He also demonstrated numerous gastric telangiectases of 3–4 mm in diameter. He died of hematemesis 1 month later. In the third family, a 48-year-old woman, Inez MWC, had recurrent epistaxis since the age of 10 and multiple telangiectases on the face. Her hemorrhaging lasted from a few minutes to half an hour. Sir William Osler was quite fascinated by this hereditary disease and published other new case reports 6 years later [10] in which he also emphasized the curious relationship of angiomata or telangiectases with abnormalities of the liver.

These reports were followed by further descriptions by Frederick Parkes Weber in *The Lancet* in 1907; thus the

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[1]Synonyms for hereditary hemorrhagic telangiectasia: Babington's disease, Sutton's disease, Goldstein's heredofamilial angiomatosis, Osler's disease, Osler–Rendu–Weber syndrome, angioma hemorrhagicum hereditaria, familial hemorrhagic telangiectasia, multiple hereditary telangiectases with recurrent hemorrhage.

eponym 'Rendu–Osler–Weber syndrome' [11] was established to identify this disease. The term 'hereditary hemorrhagic telangiectasia', an accurate description of the most common clinical features of the illness, is attributed to F.M. Hanes [12,13], a house physician at the John Hopkins Hospital in 1909. In 1921, Hyman Isaac Goldstein confirmed the presence of this familiar syndrome characterized by multiple telangiectases of the skin and the oral, nasal and gastrointestinal mucous membranes, in agreement with previous reports [14]. After Isaac Goldstein, interest in HHT increased and numerous papers were published describing the systemic involvement of HHT patients.

Throughout the years, HHT has also been called by different names according to different authors or clinical features.[1] In the period 1921–1960, more than 90 papers consisting of case reports, original articles and reviews were published [15]. When we recently conducted an electronic database search on Medline (1966–2004), PubMed (1950–2004), CINAHL (1982–2004) and EMBASE (1988–2004) entering the keywords 'Osler–Weber–Rendu' and other terms, such as HHT, hereditary hemorrhagic telangiectasia, the result was a total of 1641 publications on this disease.

A rare and misdiagnosed disease

HHT is still often misdiagnosed in affected individuals and many physicians are not familiar with the entire spectrum of its manifestations, a common problem for rare diseases. A survey of patients with rare diseases, conducted in 1988 by the National Commission on Orphan Diseases of United States Department of Health and Human Services, revealed that 50% of the patients were received a diagnosis of their disease within 1 year while for one-third it was necessary to wait from 1 to 5 years, and 15% of patients went without a diagnosis for 6 years or more [16]. A disease is considered rare in the United States when it affects one individual per 1250 and in Europe one individual per 2000; the greatest barrier to their prevention, diagnosis and treatment is inadequate knowledge [17]. Rare diseases represent about 10% of all human medical illnesses and infirmities. Once a diagnosis of rare disease, such as HHT, is established, one of the major complaints of patients is the difficulty to obtain pertinent information on the cause, symptoms, and either established or experimental treatments. In addition, the field of rare diseases is not appealing to basic or clinical investigators for several reasons: it is difficult to find adequate animal models for many rare diseases; clinical trials require more patients than those available; financial support is lacking – all this despite the fact that the history of medicine reveals that many breakthroughs in clinical sciences have been achieved as the result of studies and discoveries on rare diseases [18]. One of the most difficult issues to address when studying rare diseases pertains to the identification and recruitment of a sufficient number of patients for a given disease. A database of collaborative patient groups now represents a necessary tool to find potentially eligible patients for clinical studies. Furthermore, collaboration with similarly interested groups of scientists provides a more feasible possibility to organize such projects in a multicenter design.

Diagnosis of HHT in specialized centers

For the forementioned reasons, in recent years centers have been developed in which the physicians interested in all aspects of HHT are working to develop better therapeutic approaches. Recent progress in the field of genetics has also permitted the identification of many gene mutations, thus facilitating the characterization of the at-risk members of the same family [19]. Advancements have also been made in the treatment of HHT, which is extremely complex because of the involvement of multiple organs. The importance of a multidisciplinary approach for evaluation of morbidity (arteriovenous malformations) and concomitant complications is evident.

Due to the enthusiastic and untiring efforts by Dr Robert J. White, founder of the first center dedicated to HHT, the Vascular Malformation Clinical and Research Group at Yale University, special multidisciplinary HHT centers have been developed in North America as well as in Europe and Asia (http://www.hht.org), in which coordinated teams of experts with extensive experience with HHT collectively care for these patients. Furthermore, a HHT International Foundation was formed in 1990 (a) to foster an exchange of information concerning the diagnosis and treatment of HHT, (b) to raise funds for genetic and clinical research and (c) to sponsor special scholarships for studies pertaining to HHT. A multidisciplinary approach is made possible by the involvement of physicians who are specialized and trained in all aspects of HHT (otolaryngologists, geneticists, radiologists, hematologists, pneumologists, cardiologists, dermatologists, psychiatrists) [20]. In all the HHT centers, the initial patient visit permits the screening of patients based on their familial medical history, symptoms and typical signs by means of a physical examination. It is also essential to become acquainted with the patient's family history, to reconstruct the family pedigree and to screen the affected families.

Epistaxis and the family history together permit the detection of patients potentially affected by HHT. The patients with known genetic mutations or clinically suspected familial HHT are then subjected to complete clinical screening. Screening programs are aimed at pre-symptomatic detection of arteriovenous malformations in the brain or lung and should be recommended for all HHT patients and their relatives at-risk, even in the absence of signs and symptoms of visceral localizations, in order to reduce morbidity and mortality and to avoid serious consequences which may result if visceral arteriovenous malformations, particularly in the cerebral and pulmonary circulation, are left unrecognized and untreated [21].

The study of hepatic fistulas is carried out by means of an echo-color Doppler of the portal system [22]. Contrast echocardiography is used to investigate pulmonary shunts [23,24]. Brain magnetic resonance imaging is performed in order to locate cerebral arteriovenous malformations, whereas

gastrointestinal endoscopy and eventually videocapsule endoscopy are used to diagnose gastrointestinal telangiectases [25,26].

Pulmonary angiography are fundamental for those patients requiring trans-catheter embolotherapy, which represents the best therapeutic approach to pulmonary involvement [27]. The study of HHT patients must be completed by molecular genetic testing and psychological evaluation. The more the specialized center is multidisciplinary, the more complete the screening approach will be; often there are differences among the screening procedures in the various centers. At present, for example, there is no consensus concerning the need to screen for hepatic manifestations.

HHT is not susceptible to cure due to the current inability to perform gene therapy. Therefore the treatment of HHT patients should aim at the control of the local and systemic symptoms and the prevention of complications, thereby guaranteeing an acceptable lifestyle both at the functional and psychological level.

Genetic aspects

HHT is a heterogeneous disorder divided into two clinically indistinguishable forms: HHT-1 is caused by mutations in endoglin gene mapping on chromosome 9q [28] while HHT-2 is caused by mutations in ALK1 mapping on chromosome 12q [29]. The presence, severity and age of onset of the different manifestations vary considerably even among members of the same family who share the same underlying mutation, thus making clinical diagnosis difficult in some cases, especially in young subjects. Penetrance is strongly age-dependent, becoming almost complete by the age of 40 [30].

McAllister *et al.* [28] identified endoglin as the HHT-1 responsible gene. Endoglin is a homodimeric disulphide-linked integral membrane glycoprotein of M_r 180 000, first identified in human pre-B HOON leukemic cells [31] and named CD105. It is mainly expressed in the endothelial cells of all vessels [32], including capillaries, veins and arteries in adult and embryo human tissues as early as 4 weeks of development, but its expression is also significantly detectable on a subset of normal pre-B cells [33] and on activated monocytes [34]. The high expression of endoglin on the endothelial cell surface, together with the discovery that this molecule binds TGF-β1 and TGF-β3 to form a signaling heteromeric complex for such ligands, led to the suggestion that HHT lesions tend to arise because of the poor ability of patients' endothelial cells to take part in the TGF-mediated vascular remodeling induced by such possible stimuli as blood flow increase, wound healing, thrombus formation, local inflammation or other vessel wall stresses. TGF-β is known to be a powerful mediator of vascular remodeling through the modulation of cellular migration and adhesion, extracellular matrix synthesis and through the regulation which it exerts on the cells of the vessel wall, such as endothelial cells, smooth muscle cells, stromal cells, fibroblasts and pericytes [35].

Genetic linkage studies identified a second locus, named HHT2, on the pericentromeric region of chromosome 12q. As ALK1 belongs to the TGFβ-superfamily receptor group and shows a highly restricted expression pattern which parallels that of endoglin (it is almost exclusively expressed in endothelial cells and very few other cell types) [36], it was identified as the HHT2 gene. Recent papers have reported a specific expression for ALK1 in the endothelial cells of arterioles, but not in venules, during angiogenesis in response to vessel wall injury [37]. Such discovery indicated a role for ALK1 in the specific differentiation of newly formed arterioles and venules and suggested that mutations in ALK1 might hamper the interaction between membrane proteins which function as specific markers of either arterioles or venules, thus leading to angiogenetic impairment and HHT lesions. The nature of the ALK1 and endoglin interaction, and the reason why these genes cause the same clinical phenotype (both in men and in mice) are still completely obscure. Among the different hypotheses proposed, the most recent [38] arose from the observation that both ALK1 and endoglin mutations reduce endoglin expression levels on patients' activated monocytes in comparison with to age-matched controls. The authors proposed that, due to ALK1-mediated endoglin expression stimulation, mutations in either genes result in the same biochemical defects.

As HHT is an autosomal dominant disease, patients are expected to be heterozygous for the disease-causing mutation. To date, more than 100 mutations have been reported for each of the two genes [39]. In both genes, mutations tend to be unique and family specific, which makes mutation screening costly and laborious. As seen in Fig. 1A, the ENG locus spans approximately 35 kb on chromosome 9. No mutational hot spot exists as mutations are spread over the entire length of the 15 exons, with the exception of exon 13 and 14 which encode for the transmembrane domain and the cytoplasmic tail, respectively (Fig. 1B). Most mutations are short insertions and deletions leading to premature stop codons and enzymatic degradation of the mutated mRNA (nonsense-mediated decay, NMD) [40]. Many substitutions have also been reported, the majority of which are nonsense mutations or splice-site mutations. Missense mutations and in-frame deletions account for only 20% of endoglin mutations: they are currently considered null mutations because they yield misfolded and unstable

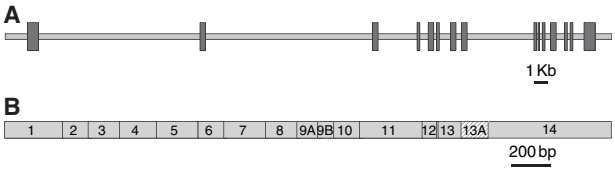

Fig. 1. (A) Endoglin exon–intron organization on chromosome 9q. Mature RNA covers 15 exons. (B) Whole CDS spans 1974 bp. Exon 13A (striped box) contains a precocious stop codon which is typical of a shorter isoform, named S-endoglin, with a similar pattern of expression as the longer isoform, named L-endoglin, with functions unknown [77].

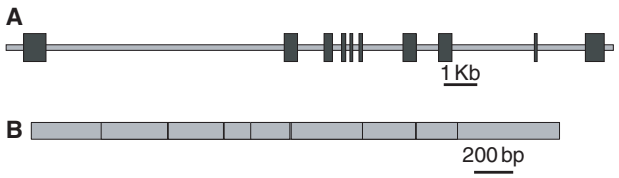

Fig. 2. (A) ALK-1 exon–intron organization on chromosome 12q. Exon 1 is non-coding, as ATG start codon falls in exon 2. (B) ALK-1 coding sequence, starting from exon 2 and ending in exon 10. ALK-1 CDS has a length of 1515 bp.

cytosolic proteic precursors, degraded intracellularly [41]. In addition, deletions and duplications encompassing more than one exon have been published [42]. As many as 80% of endoglin mutations have been observed in only one family, suggesting that most mutational events are family specific. Only four founder effects are known, all reported in the Dutch population or in the Caribbean populations of Dutch origin [43,44]. The great majority of endoglin mutations account for familial cases, but *de novo* mutations have been reported which are responsible for sporadic cases but they have also been demonstrated to be transmitted to the offspring [19,45].

The ALK1 gene spans 10 exons on chromosome 12q13. (Fig. 2A,B). The first exon of ALK1 is non-coding, but it is enclosed in a 9.2 kbp-long fragment, which includes the gene promoter and its whole intron 2 containing DNA sequences essential to ensure the specific ALK1 expression on arterial cells of the endothelium [46]. Mutations have been reported only in the nine coding exons and tend to clusterize in exon 3, exon 7 and exon 8 (even if mutations are also present in the other coding exons). Exon 2 and exon 3 encode for the extracellular and ligand-binding domain, though the actual *in vivo* ligand is unknown (ALK1 is a so-called 'orphan-receptor'). Exon 6–10 encode for the cytoplasmic portion, which has a documented serine-threonine kinase activity on SMAD1 and SMAD5 proteins which are well-known intracellular effectors involved in the TGF-β-BMP signalling pathway [47]. Two-thirds of ALK1 mutations are missense mutations: it is still unknown whether or not they can yield a mature membrane protein with impaired kinase activity and/or ligand binding capacity. The existence of dominant-negative alleles cannot even be ruled out. Unlike that in the endoglin gene, very few splice-site mutations have been reported in ALK1, and no large deletions–duplications. Only two founder effects have been demonstrated in ALK1 thus far, but the number of mutations reported in different families, due to distinct mutational events, is greater than those of endoglin gene. Several point mutations in ALK1 occur in CpG dinucleotides hot spots, consisting of a transduction in either base pair, presumably through a methylation–deamination mechanism involving the cytosine of either coil [48]. Nonetheless, apart from the aforementioned exceptions, the majority of ALK1 mutations are family specific as in the endoglin gene, requiring an extensive mutation screening all along the gene. However, screening on probands is often initially performed on exon 3, exon 7 and exon 8, because they are mutation-rich exons (see above). The list of different types of mutations of both genes are reported in Table 1.

A possible third locus has been hypothesized after Wallace *et al*. reported a family unlinked to either endoglin or ALK1 presenting an uncommon extensive pulmonary involvement [49]. To date, this third locus has not been definitely identified, but it appears to be located on chromosome 5 [50]. On the other hand, the recent discoveries of unusual TGF-β-mediated pathways [51,52] which do not transduce signals through SMAD proteins (important intracellular proteins possessing homologous domains to the *Drosophila melanogaster* MAD protein), exemplify how complex cross-talk interactions occur in cells, and suggest that there are still unknown possible interactions of endoglin and ALK1 with other proteins which may be capable of triggering different cascades downstream.

Like all autosomal dominantly inherited diseases, patients who carry the disease-causing mutations have a 50% probability to transmit it to each of their offspring. Compatibility with life of the homozygous state is a controversial issue, given the scarce number of reports in the literature [53]. In 1944, a child born from two HHT-affected individuals died at the age of 11 weeks due to severe hemorrhages; therefore, it was hypothesized that the child was homozygote as she was affected with multiple telangiectasic hemangio-endotheliomas involving skin, mucosa and internal organs. In 1978, a presumed homozygote was identified in a large family in which both parents were affected, as also were all the 13 children [54]. At present, there is only one molecular investigation of a large Arab family with a high level of consanguinity. No live homozygous individual for the familial endoglin mutation was found, supporting the view that endoglin mutations are, as in the mouse, lethal in homozygosity [55].

Once the mutation has been identified in the proband, prenatal diagnosis can also be performed with amniocentesis or villocentesis. The molecular diagnosis on fetuses would allow the choice of therapeutic abortion of those carrying the mutation, even though prenatal knowledge of the HHT

Table 1 A list of different types of mutations reported in the Endoglin or ALK1 genes, updated to December 2004. Mutations reported in more than one family were counted only once in the list

Gene	Missense	Nonsense	Insertion/deletion	Splicing	Gross deletions	Gross duplications	Total no. of mutations
Endoglin	29	20	67	22	7	2	147
ALK1	54	15	32	5	–	–	106

mutation is more important for monitoring of visceral AVMs, avoiding potentially severe complications both during pregnancy and during delivery.

Symptoms and treatment of the disease

Nose

Nosebleeds are the most common cause of emergencies and when massive their treatment is challenging for physicians. Epistaxis significantly compromises the quality of life of the affected persons, thus justifying the multiple efforts to find a definite therapy for this symptom [56]. In the presence of epistaxis it may be useful to consider such therapeutical options as the administration of tranexamic acid at high doses (1 g per three times daily, orally or i.v. at the time of epistaxis) [57] or combined estrogen–progesterone preparations [58] to avoid hasty nasal tamponades which can lead to further damage of the mucosa of these patients. If these measures are insufficient and the frequency and duration of epistaxis impair the patient's quality of life, a photocoagulation laser or a septal mucosal dermoplasty can be recommended [59]. Embolization of the external carotid artery branches can be performed for acute relief of symptoms, although it is ineffective for long-term management and can cause complications related to ischemia [60]. Chemical cauterization should always be avoided because it may harm nasal structures (Fig. 3). In the presence of anemia, oral iron supplementation or more rarely, blood transfusion may be required.

Skin

Telangiectases of the skin and mucosae are generally observed after the age of 30 years; they are commonly found on the lips, tongue, palate, fingers, face, conjunctiva, trunk, arms and nail folds. Bleeding from these telangiectases may occur, but it is rarely clinically important; however, patients frequently request medical or laser treatment for cosmetic reasons [61]. Laser therapy can also be considered for treatment of painful cutaneous telangiectases [2].

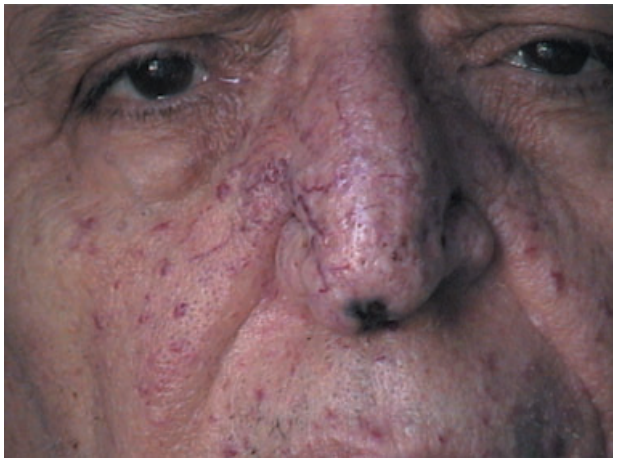

Fig. 3. Typical facial telangiectasia in a 64-year-old HHT patient with a deformed nose due to multiple inappropriate surgical procedures (nasal tamponade and catheterizations) for recurrent severe epistaxis.

Brain

Generally, most neurological symptoms in HHT depend on pulmonary arteriovenous malformations, but it is not uncommon that seizures, epilepsy or paraparesis mask the presence of vascular malformations in the central nervous system (brain, meningi and spinal cord). Cerebral vascular malformations are associated with HHT in only 10% of patients; on the other hand, the prevalence of cerebral vascular malformations among HHT patients is 2.3% but a much higher prevalence is observed when asymptomatic patients are screened [1]. Transcatheter or stereotactic arteriovenous embolotherapy might be necessary in the case of cerebral fistula, depending on its localization, form and size, while arteriovenous pulmonary malformations 3 mm or greater in diameter are currently treated [62,63].

Lungs

Pulmonary arteriovenous malformations are present in about 30% of patients, occasionally leading to hemoptysis and hemothorax and more rarely to a fatal outcome. The bleeding complications of pulmonary arteriovenous malformations are more common during pregnancy [64], most likely due to the increased circulating blood volume, thus representing an indication for screening for malformations in HHT women or in those with a first-degree HHT relative before pregnancy. The occasional discovery of pulmonary arteriovenous malformations, especially when multiple, should suggest a diagnosis of HHT, as approximately 70% of all pulmonary arteriovenous malformations are found in HHT (Fig. 4A).

The most frequent symptoms and complications of pulmonary arteriovenous malformations are a consequence of right-to-left shunts. Patients are often asymptomatic but dyspnea is quite common. The presence of pulmonary malformations can be also suggested by cyanosis, clubbing, vascular bruit, polycythemia and pulmonary hypertension. Sometimes, despite minimal respiratory symptoms, patients may present sudden neurological complications, such as transient ischemic attacks, stroke, and brain abscess as the latter are due to paradoxical embolization of thrombotic or bacterial emboli originating in the venous circulation which bypass the normal filtering system of the pulmonary capillaries, enter the arterial circulation, and occlude arteries in the various organs. The risk of cerebral complications increases with the multiplicity of pulmonary arteriovenous malformations; in fact, the prevalence of ischemia or brain abscesses ranges from 46% among patients with a single pulmonary arteriovenous malformation to 59% in those with multiple pulmonary malformations and up to 70% among those with pulmonary malformations of the diffuse type [24]. At least 10% of HHT patients are expected to

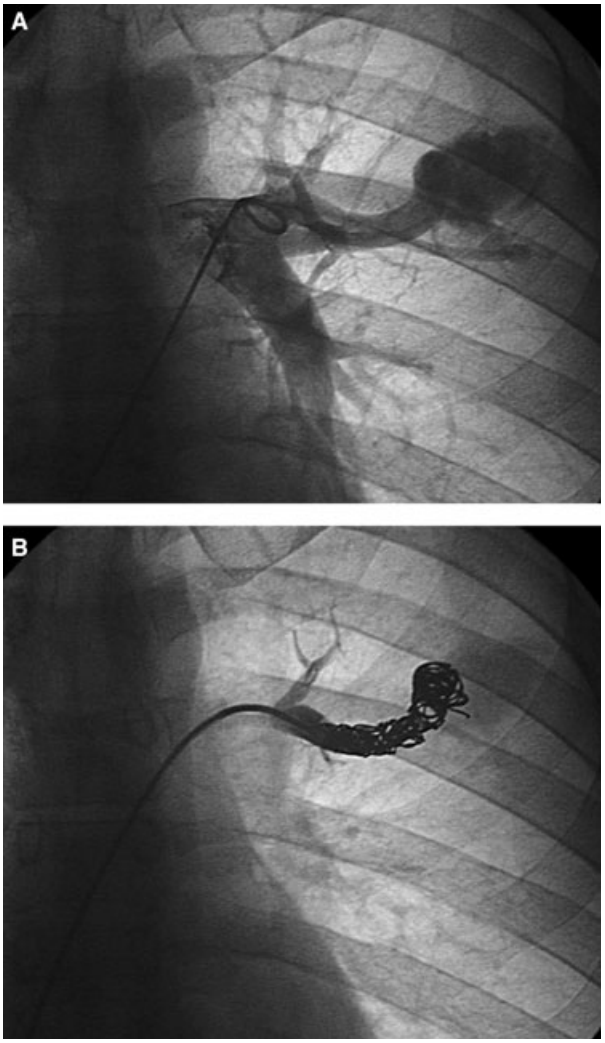

Fig. 4. (A) A large arteriovenous malformation in the left lung of an HHT patient. (B) The same arteriovenous malformation after ebolization with steel coils (courtesy of Dr A. Bortone).

have a brain abscess during their lifetime [65]. For this reason it is important that HHT patients with pulmonary arteriovenous malformations receive antibiotic prophylaxis prior to dental and surgical interventions, thereby reducing the risk of embolic abscesses which may potentially affect all organs but most frequently the brain, the spleen and the liver [2].

Primary pulmonary hypertension must also be considered another serious, though quite rare, complication associated with HHT. It is known that this familial condition is an autosomal dominant disease caused by mutations in the BMPR2 gene belonging to the TGF-β superfamily type II receptor group. In fact, the identification of some members of HHT2 kindreds sharing both pulmonary arterial hypertension and classical HHT features lead to the hypothesis that both BMPR2 and ALK1 are involved in the pathogenesis of pulmonary arterial hypertension. It has been proposed that mutations in ALK1 may disrupt two distinct patterns of pulmonary arterial endothelial cell development, the former causing dilated vessels followed by the pulmonary arteriovenous fistulae typical of HHT disease, and the latter leading to the classical occlusions of pulmonary arterioles commonly arising in BMPR2 mutation carriers and responsible for pulmonary arterial hypertension [66]. This condition does not seem to be associated with endoglin HHT-causing mutations, except for a recently reported case characterized by the onset of pulmonary arterial hypertension after dexfenfluramine-based treatment [67].

Liver

Liver involvement in HHT may also be silent, as the majority of patients remains asymptomatic throughout their lifetime. Recently, the clinical settings of liver involvement in HHT have been better classified and at least four different patterns have been described, depending on the type of shunt present. An anastomosis between the hepatic artery and hepatic veins leads to a high-output heart failure. This clinical pattern is generally characterized by shortness of breath without anemia, and clinically significant pulmonary malformations. Vascular hyperkinesias without heart failure (tachycardia and palpitation) or acute pulmonary edema may also be observed. Cardiac auscultation usually reveals systolic murmurs, occasionally associated with a third bruit, whereas non-cirrhotic hepatomegaly can be found at palpation together with a systolic murmur on auscultation. Right heart catheterization confirms the elevation of cardiac output and pulmonary–capillary wedge pressure [68].

A shunt from the hepatic artery to the portal vein is responsible for portal hypertension with a possible onset of hematemesis, melena and ascites. On the other hand, these shunts have not been described in all HHT patients with portal hypertension, suggesting that an alternative explanation exists for this complication. It has been hypothesized that the liver undergoes nodular transformations also known as 'pseudocirrhosis': the chronic ischemia causes atrophy of the liver acinus, whereas adjacent acini undergo compensatory hyperplasia resulting in micronodularity and portal hypertension. The sonographic aspects of the liver mimic those of cirrhosis, leading to an unnecessary liver biopsy which represents a dangerous procedure for these patients as the vascular malformations may bleed [68].

Portosystemic encephalopathy can occur when portal vein-hepatic vein shunts are present or in the setting of portal hypertension due to pseudocirrhosis or classic cirrhosis. Another clinical presentation of the liver involvement in HHT is anicteric cholestasis, probably due to hypoperfusion of the peribiliary plexus; it is characterized by serum values of γ-glutamyl transferase and alkaline phosphatase from two to nine times the normal value. Patients may also have pain in the right upper quadrant, jaundice and fever. Ischemic cholangitis may also occur as a consequence of hepatic embolotherapy and is the most common clinical pattern leading to orthotopic liver transplantation [69].

Recently, liver involvement has been assessed by multidetector row helical computed tomography, 74% of patients

Table 2 Clinical features of hereditary hemorrhagic telangiectasia

Anatomical alterations	Site	Average prevalence (%)	Clinical signs, symptoms and complications
Telangiectases	Skin	85	Cosmetic considerations (especially on the face)
	Mucosa	97	Spontaneous bleeding (nose, oral cavity, gastrointestinal, urethra) Digestive tract bleeding Iron deficiency anemia
Arteriovenous malformations	Lung	30	Respiratory failure, hemothorax, brain abscess
	Liver	75	Cholestasis, cirrhosis, portal hypertension, cardiomyopathy, congestive heart failure
	Brain and spinal column	6	Syncope, cefalea, seizures, epilepsy, stroke
	Retina, kidney, prostate, spleen	Not known	Bleeding

Table 3 Therapy for clinical manifestations of HHT

Clinical manifestations/complications	Treatment
Epistaxis	Hygienic health norms (adequate environmental humidity, daily use of nasal lubricants) Tranexamic acid (orally and/or intravenously) Estrogen/progesterone preparations Laser photocoagulation Dermoplasty of nasal mucosa Embolization of nasal arteries To be avoided: physical stress, nasal trauma, use of vasodilatators, aspirin and other non-steroid anti-inflammatory agents
Anemia	Iron therapy (oral or intravenous) Blood transfusions when necessary
Cutaneous telangiectases	Laser therapy
Gastrointestinal telangiectases	Estrogen/progesterone therapy Danazol Octreotide Thermic cauterization Laser photocoagulation by endoscopy
Hepatic arteriovenous malformations	Organ transplant when severe hepatic insufficiency is present
Pulmonary arteriovenous malformations	Transcatheter embolotherapy with balloon or steel coils (Fig. 4B)
Cerebral arteriovenous malformations	Transcatheter embolotherapy Stereotaxic radiotherapy

presenting hepatic vascular abnormalities. Arterioportal shunts were present in 52% patients, arteriosystemic shunts in 15% and both types of shunt in 33% [70]. Treatment of hepatic fistulae is often not necessary because there is a risk of acute liver necrosis in case of embolotherapy, even if some German authors have presented the successful results of a prospective study of staged hepatic artery embolization [71]. When hepatic fistulae cause complications or in very severe liver insufficiency, organ transplantation remains the treatment of choice [72,73].

Digestive tract

Mucosal telangiectases located in the digestive tract have a more grave significance because they can lead to severe bleeding late in life. They affect 13–33% of HHT patients of whom 50% require blood transfusions [27]. Unfortunately, the therapeutic options, such as argon-plasma coagulation or administration of such drugs as estrogens or octreotide are often unable to sensibly reduce the frequency and severity of bleeding and hence episodes of major bleeding in HHT patients have a negative prognostic value [74]. In case of gastrointestinal bleeding, drug therapy with estrogen–progesterone preparations, danazol and octeotride is sometimes successful in reducing the necessity of blood transfusions. Thermal or laser cauterization by endoscopy may be also performed [25] but endoscopic procedures are palliative especially when multiple lesions are present and future research must be oriented toward systemic medical therapies (Tables 2 and 3).

Interestingly, Gallione *et al.* [75] have recently reported that mutations in the MADH4 gene, which is held responsible for juvenile polyposis (an autosomal dominant disorder without any phenotypical traits overlapping with HHT), can also determine arteriovenous malformations, both in digestive tract and in other organs, which are usually associated with mutations in ENG and ALK1, the two known HHT-causing genes. The authors concluded that both ENG and ALK1 genes transduce a yet-unknown TGF-mediated signal through SMAD4, the protein encoded by the MADH4 gene. Mutations that disrupt the SMAD4 function would then potentially impair the ENG and/or ALK1 signal capacity, thus leading to

a combined syndrome of juvenile polyposis and HHT. Consequently, families or individuals affected by HHT but negative to ENG and ALK1 mutation screening, might carry a mutation in the MADH4 gene and potentially be also at risk for juvenile polyposis.

Conclusions

Recent progress in molecular genetics of HHT has permitted the identification of many gene mutations, thus facilitating the characterization of family members at risk for the disease. However, until genetic diagnosis is possible in all HHT centers, imaging techniques represent the only essential support to clinical data for the identification of all affected persons. Screening with diagnostic imaging can supply the third criterion necessary for HHT diagnosis (visceral arteriovenous malformations) in addition to detecting those vascular malformations which may require treatment.

Multidisciplinary HHT centers have been established throughout the world and, with the cooperation of the HHT International Foundation, a program of training for HHT patients has been organized which consists in annual meetings between patients and physicians in order to suggest the main health measures meant to improve the quality of life and reduce the feeling of isolation due to patients' awareness of their rare disease.

The understanding of HHT is rapidly expanding. The discovery of genetic heterogeneity may help to better understand the natural history of the disease as the incidence of the clinical manifestations may vary widely. Multicenter cooperation may also lead to randomized, prospective trials to determine the efficacy of various therapies. The identification of the disease-causing mutation in families with HHT would permit the molecular diagnosis in first-degree relatives of clinically affected individuals, thus making a pre-symptomatic diagnosis a reality. Moreover, individuals not carrying the familial mutation can avoid extensive and costly clinical instrumental procedures. Therapeutic advances, including gene therapy, may be developed in the future, given the ease of access through the bloodstream to endothelial cells, the target tissue. Better understanding of HHT may also increase critical insights into other diseases involving vascular damage and repair. Finally, perhaps Osler's hope [76] will be fulfilled: 'To wrest from nature the secrets which have perplexed philosophers in all ages, to track to their sources the causes of disease, to correlate the vast stores of knowledge, that they may be quickly available for the prevention and cure of disease, these are our ambitions'.

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