OSLER-WEBER-RENDU SYNDROME (HEREDITARY HEMORRHAGIC TELANGIECTASIA)

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Introduction and eponyms of the disease

Osler-Weber-Rendu syndrome, also known as "Rendu-Osler-Weber disease", "Osler's disease" or "hereditary hemorrhagic telangiectasia (HHT)", was first described more than a century ago as a rare condition producing minor discomfort for affected people. Nowadays, this disorder is considered to be more common than previously thought, and its association to brain, liver and pulmonary lesions are sources of substantial morbidity and mortality and represent even these days a continuing challenge for many sub-specialities (Guttmacher et al. 1995).

Historical perspective

It is still discussed controversially whether it was Sutton in 1864 who was the first to report on HHT as a disorder of epistaxis and degeneration of the vascular system. One year later, Babington was said to have noted a possible familial relationship saying that the occurrence of nosebleeds could be inherited (Babington 1865). Over the years, recurrent epistaxis concurrent with "petits angiomes cutanes et muqueux" was again described by Rendu in 1896 (Rendu 1896) as well as in 1901 by Sir William Osler who reported on a family with recurrent epistaxis as well as skin and mucous membrane telangiectases (Osler 1901). In 1907, Weber followed with his description of multiple hereditary angiomata associated with recurrent haemorrhage (Weber 1907). The term hereditary hemorrhagic telangiectasia (HHT) was finally attributed to Hanes, who wrote on "multiple hereditary telangiectases causing haemorrhage" in 1909 (Hanes 1907). The typical clinical triad with characteristic multiple telangiectases, recurrent nosebleeds and familial occurrence have become firmly established as a medical entity.

Incidence and prevalence

Hereditary hemorrhagic telangiectasia occurs with a wide geographic distribution among many ethnic and racial groups, but white patients are primarily affected. Men and women are affected equally. In previous studies, the incidence of the disease was estimated at 1–2 in 100.000 (Garland and Anning 1950). However, the HHT prevalence nowadays shows to be more frequent than formerly thought. Recent careful epidemiologic studies in France, Denmark and Japan reveal an incidence of 1 in 5–8000 (Bideau et al. 1989, Kjeldsen et al. 1999, Dakeishi et al. 2002).

Clinical manifestations

Nose

Spontaneous recurrent nose bleeds from telangiectasia of the nasal mucosa are the most common clinical manifestation of HHT. In more than 90% of cases they represent the first clinical symptom of the disease (Römer et al. 1992) (Fig. 1). However, while some patients experience significant nosebleeds on a daily basis leading to chronic anaemia, others will have only occasional nosebleeds (Aassar et al. 1991). Recurrent epistaxis begins in more than 50% before the age of 20 (Haitjema et al.

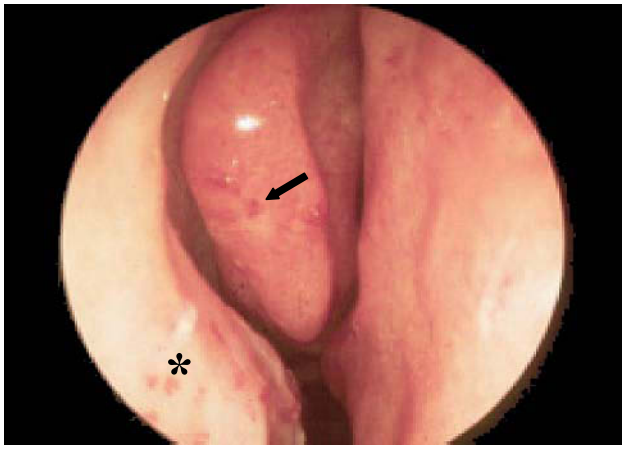

Fig. 1. Left nasal cavity with multiple telangiectasia on the head of the inferior turbinate (arrow) and the anterior part of the nasal septum (asterisk).

1995, 1996). The onset of clinical manifestation has been described in many cases by the age of 10, and in most cases by the age of 21, becoming more severe in later decades in about two thirds of affected individuals.

Skin

Muco-/cutaneous telangiectases occur in about 50–80% of individuals. As already described by Rendu in 1896, they appear as "small purplish stains", of the size of a pinhead, the largest reaching the size of a lentil. In general, these lesions manifest later in life than epistaxis, but typically arise during youth, with most cases developing these lesions at the third or even forth decade of life, and increasing in size and number with age (Plauchu et al. 1989). They mostly occur on the face, lips, mouth, tongue and buccal mucosa, ears, hands, fingertips and chest in descending order of frequency and in any combination, but can also occur elsewhere (Figs. 2–5). They may bleed but this is rarely clinically significant and the main concern is rather cosmetic (Guttmacher et al. 1995).

Lung

Pulmonary arteriovenous malformations consist of direct connections between a branch of a pulmonary artery and a pulmonary vein through a thin-walled aneurysm. They are often multiple and appear in both lungs, with a predilection for the lower lobes. It is estimated that approximately 60–70% of pulmonary arteriovenous malformations (pAVM) occur in patients with HHT (Dines et al. 1974, Schneider et al. 2008). Therefore, their detection should

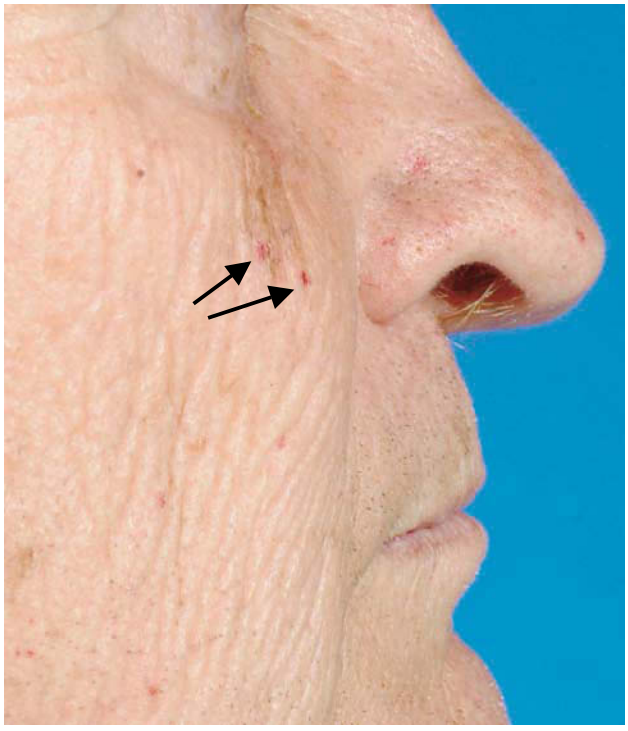

Fig. 2. Manifestation of cutaneous telangiectasia (⟶) on the face of an HHT patient.

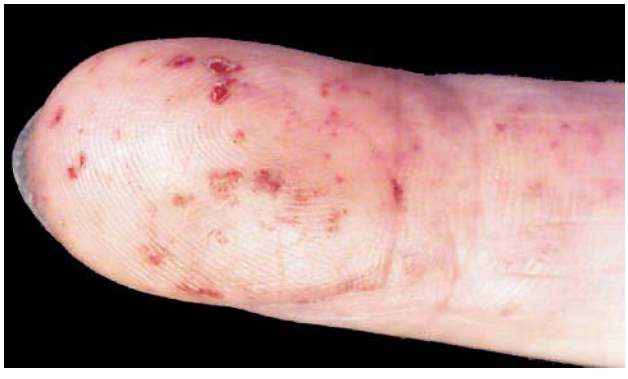

Fig. 3. Manifestation of cutaneous telangiectasia on the right forefinger of an HHT patient.

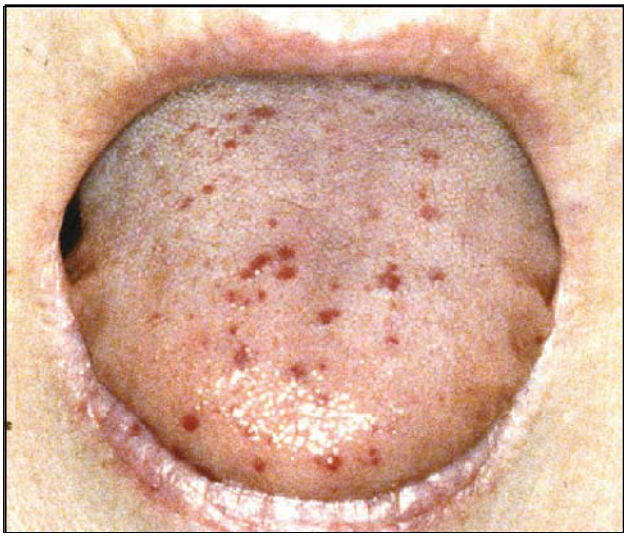

Fig. 4. Typical sight of an HHT patient with clinical manifestation of mucocutaneous telangiectases on the tongue.

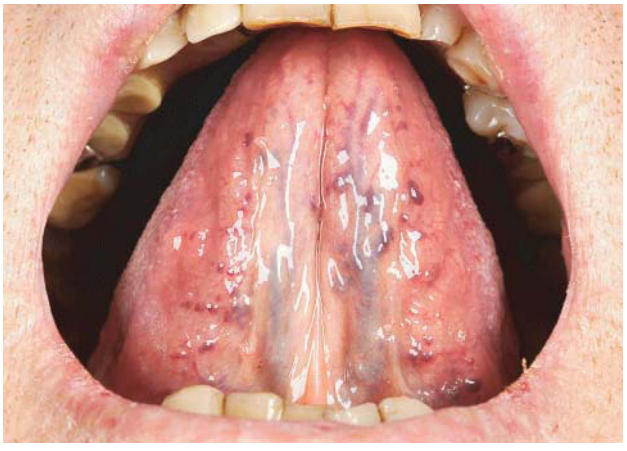

Fig. 5. Front view into the oral cavity with few mucocutaneous telangiectasia below the tongue.

prompt a thorough review of the patient and his or her family. The incidence of pAVM apparently varies according to the specific gene for the condition that is present (Kjeldsen et al. 2000). The HHT subgroup with endoglin mutations has a higher risk (40%) than HHT patients with ALK1 mutations (Mc Allister et al. 1994, Porteous et al. 1994). Pulmonary AVMs tend to increase in size, especially if multiple, and rarely regress spontaneously (Bosher et al. 1959, Sluiter-Eringa et al. 1969, Vase et al. 1985). In female, pAVM have been reported more often than in males. During the course of pregnancy, pAVMs also increase in size and can cause severe complications (Shovlin et al. 1995). Therefore, female patients with HHT need a thorough screening for pAVMs before pregnancy or need to be categorized as patients with a "high risk pregnancy" who need strict follow-up examinations (Shovlin et al. 1995, Shovlin and Letarte 1999). The mortality rate in untreated but usually symptomatic patients with pAVMs range from 4 to 22% (Dines et al. 1974, Shovlin and Letarte 1999), in severe cases even up to 40% (Stringer et al. 1955). The abnormal vessels can bleed into the bronchus or the pleural cavity, sometimes with a fatal outcome (Muri 1955). The direct communication between the pulmonary and systemic circulation, bypassing the capillary bed, with their functional consequences are the most commonly caused problems. Such right-left-shunts cause hypoxaemia and the absence of a filtering capillary bed allows embolism which can reach the systemic arteries, inducing clinical sequelae especially in the cerebral circulation with brain abscesses and stroke. These processes account for the clinical features such as dyspnoea, fatigue, haemoptysis, cyanosis or polycythemia (Burke et al. 1986). Small pAVMs with shunting of less than 25% of pulmonary blood flow are asymptomatic in half of the cases. These patients show no cyanosis but demonstrate dyspnoea on exertion and easy fatigability. Additionally, a possible correlation of HHT with pulmonary hypertension is been discussed (Shovlin and Letarte 1999). The histological and pathophysiological features of HHT and primary pulmonary hypertension seem to be different. Pulmonary arteriovenous dilatation is the hallmark of lung involvement in hereditary hemorrhagic telangiectasia, leading to decreased pulmonary vascular resistance and increased cardiac output, with normal to low pulmonary arterial pressure. In contrast, primary pulmonary hypertension is characterized by obliteration of small pulmonary arteries, leading to increased pulmonary vascular resistance, marked elevation of pulmonary arterial pressure, and ultimately, a reduction in cardiac output.

Brain

Cerebral vascular malformations (CVMs) as well as most of their complications are thought to affect up to 15% of patients with HHT. Neurologic symptoms can include migraine headache, brain abscess, transient ischemic attack, stroke, seizure, and intracerebral as well as subarachnoid haemorrhage (White et al. 1988, Robin et al. 1976), and affect particularly those HHT patients who have a personal or family history of pulmonary arteriovenous malformations (Burke et al. 1986, Porteous et al. 1992, Willinsky et al. 1990, Press and Ramsey 1984, Hewes et al. 1985). In two thirds of cases, in whom neurologic symptoms develop, pulmonary AVMs are the source of the symptoms. In the remaining third, cerebral or spinal arteriovenous malformations cause subarachnoid haemorrhage, seizure, or less common paraparesis (Matsubara et al. 2000). Brain or spinal abscess, transient ischemic attack, and ischemic stroke occur particularly in patients with pulmonary AVMs who have right-to-left shunting that facilitates the passage of septic and bland emboli into the cerebral circulation (Burke et al. 1986, Maldonado et al. 2007).

GI-tract and liver

Recurrent haemorrhage of the upper or lower gastrointestinal (GI-) tract occurs in a minority of patients with hereditary hemorrhagic telangiectasia (Plauchu et al. 1989, Kjeldsen and Kjeldsen 2000). Usually, GI-bleedings do not start until the fifth or sixth decade. It often presents as an iron deficiency anaemia but occasionally as an acute gastrointestinal haemorrhage. In few cases, the coincidence of HHT with hereditary juvenile polyposis could be observed. A possible genetic association between these two disease is of major importance, as juvenile polyposis has a known high rate of possible malignancies (Reilly and Nostrant 1984).

Liver involvement with fistulas due to the presence of multiple arteriovenous malformations or atypical cirrhosis is a rare but important manifestation of hereditary hemorrhagic telangiectasia (Bernard et al. 1993, Garcia-Tsao et al. 2000). Though many patients are asymptomatic, a high cardiac output caused by left-to-right shunting within the liver can lead to heart failure. Cases with hepatomegaly, portal hypertension, biliary manifestation with pain in the right upper quadrant, jaundice as well as

Table 1. Clinical features and current diagnostic methods in HHT

Organ	Incidence	Type of lesion	Clinical symptoms	Diagnostic methods
Nose	>90%	Telangiectasia	Epistaxis	Visual inspection
Skin	50–80%	Telangiectasia	Bleeding (minor)	Visual inspection
Lung	>20%	Arteriovenous malformation	Cyanosis, Cerebral abscess, Embolic stroke, Migraine	Arterial-blood gas measurement, Pulse oximetry, Contrast echocardiography, High-resolution helical CT, Angiography
Central nervous system	15%	(Arterio-)venous malformation, AV-Fistula => especially multiple, cortical	Headache, Subarachnoid hemorrhage	MRI, MR-angiography
GI-tract, Liver	11–25% 8–16%	Angiodysplsia, Arteriovenous malformation, Telangiectasia	Bleeding, Ascites, Hyperdynamic circulation, Portosystemic shunts	Endoscopy, Ultrasound, CT

abdominal angina from a mesenteric arterial "steal" have been described (Bernard et al. 1993). Patients with clinically significant liver lesions most often present with a hyperdynamic circulation due to a shunting from hepatic arteries to hepatic veins, portal veins to hepatic veins, or both. This condition often results in pseudocirrhosis, with nodular transformations of the parenchyma without fibrous septa.

On overview on the main clinical features and diagnostic measures is given in Table 1.

Pathogenesis

The characteristic manifestations of HHT are all due to abnormalities of the vascular structure. The earliest morphologic change in the pathogenesis of HHT appears to be a focal dilatation of postcapillary venules, often surrounded by a mononuclear infiltrate. As the venules increase in size, both in luminal diameter and vascular wall thickness, they become convoluted and connect to enlarging arterioles through capillary segments. Eventually, these segments disappear, leading to the formation of a direct arteriovenous communication (Fig. 6a–c) (Braverman et al. 1990, Menefee et al. 1975). In fully developed telangiectases, most venules show excessive layers of smooth muscle cells without any elastic fibres or have an incomplete layer of smooth muscle cells. Additional defects in endothelial junctions have been described (Hashimoto and Pritzker 1972, Jahnke 1970). Whereas telangiectases appear nearly universal, arteriovenous malformations which represent the other prominent lesions of HHT, appear only at certain forms of the condition. Similar to telangiectases, these malformations lack capillaries and consist of direct connections between arteries and veins, but are much larger in size (Porteous et al. 1994). In general, HHT patients have a normal thrombocyte function and an unimpaired coagulation. However, rare cases of HHT associated with von Willebrand's disease have been described (Ahr et al. 1977).

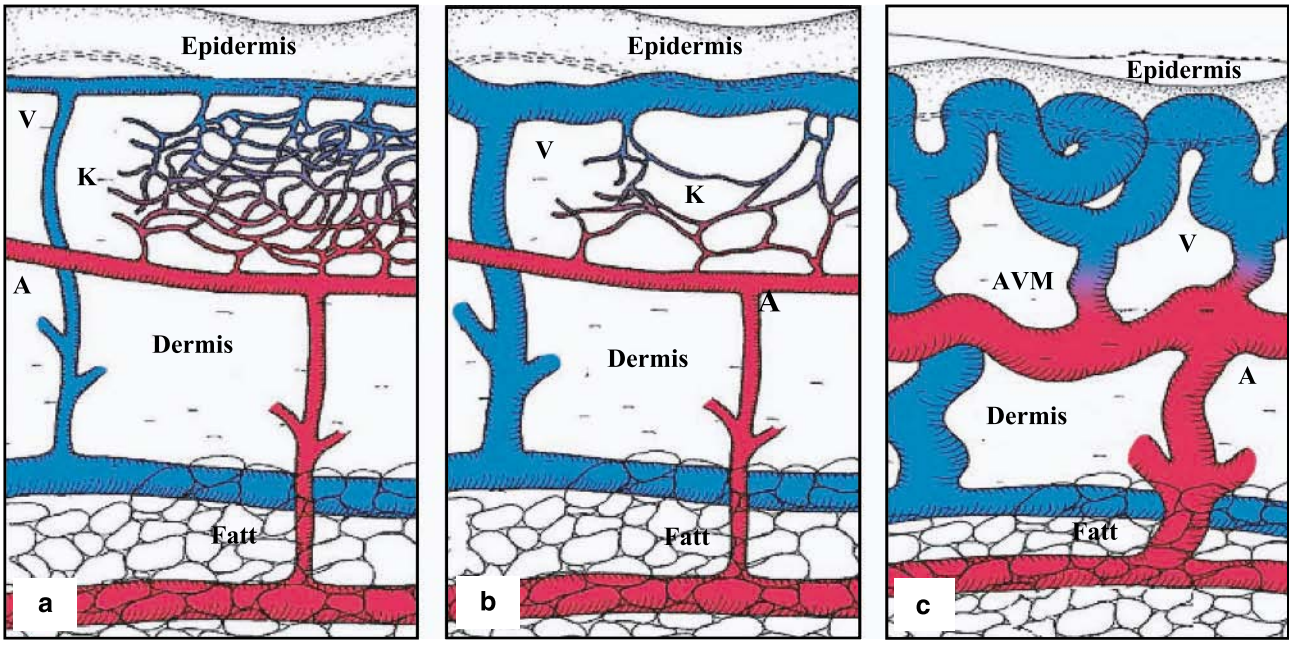

Fig. 6. (**a**–**c**) Development of telangiectasia in the region of the skin and mucosa. (**a**) Normally, arterioles (A) in the papillary dermis are connected to venules (V) through multiple capillaries (C). (**b**) In the early stage of telangiectases, the capillary bed (C) becomes more and more rare with the development of dilated venules which are still connected to arterioles through one or more capillaries. (**c**) In a fully developed telangiectasia, the venules and their braches become markedly dilated, elongated, and convoluted. The arterioles become also dilated and communicate directly with the venules without intervening capillaries.

Molecular genetics

The mode of inheritance is autosomal dominant and affected individuals are heterozygous. Homozygous forms are considered to be lethal (Snyder and Doan 1944). In HHT patients the penetrance, which is estimated at 97–100%, is age-dependent (Porteous et al. 1992). In spite of the high HHT penetrance, evidence of disease may not be present until after the age of 30 (Plauchu et al. 1989, Porteous et al. 1992). Nevertheless, about 20% of patients can have a negative familial history, indicating the occurrence of spontaneous mutations, the differences in the individual clinical manifestations or an incomplete and insufficient screening examination of all family members and relatives (Römer et al. 1992).

Mutations which cause HHT have been identified in at least two different genes. The genetic linkage to both these genes has been established on chromosome 9q33–q34 (Shovlin et al. 1994, Mc Donald et al. 1994), and on chromosome 12q (Johnson et al. 1995). The gene for HHT at chromosome 9q3 has been identified by Mc Allister and co-workers as endoglin (ENG) (Mc Allister et al. 1994). The gene encoding for HHT at chromosome 12q has been identified as activin receptor-like kinase 1 (ALK1) (Johnson et al. 1996). In HHT type 1, chromosome 9q33–q34 mutations alter the coding sequence of endoglin, whereas in HHT type 2, chromosome 12q mutations alter the coding sequence of ALK1. Previous studies could demonstrate that subjects with known endoglin mutations have an incidence of pulmonary arteriovenous malformations of approximately 30%, but that the incidence is less than 5% in subjects in whom the endoglin locus had been excluded (Berg et al. 1996). Endoglin and ALK1 encode proteins which are expressed on vascular endothelial cells and are involved with signalling by the transforming growth factor beta (TGF-β) superfamily.

A possible correlation of HHT with familial juvenile polyposis (FJP) is discussed. Familial juvenile polyposis is characterized by the appearance of juvenile polyps in the gastrointestinal tract. Patients with this syndrome are at an increased risk for cancer of the colon, stomach, and pancreas. Similar to HHT, familial juvenile polyposis is an autosomal dominant disorder. It is caused by mutations in the MADH4 gene, encoding proteins which are also involved in the transforming growth factor-beta signalling pathway.

In addition, primary pulmonary hypertension (PPH) has also been reported in association with hereditary hemorrhagic telangiectasia type 2. PPH, an autosomal dominant progressive disease, is characterized by plexiform lesions of endothelial cells in pulmonary arterioles in which widespread occlusion of the smallest pulmonary arteries leads to increased pulmonary vascular resistance, and subsequently right ventricular failure. The gene for PPH encodes bone morphogenetic protein receptor II (*BMPR2*), located on human chromosome 2, which is also a member of the transforming growth factor superfamily of receptors.

Diagnosis of HHT

Diagnosis of HHT is made clinically by the Curaçao criteria which were established in June 1999 by the Scientific Advisory Board of the "HHT Foundation International Inc." to standardize research and to improve the management of individuals with HHT (Shovlin et al. 2000). The criteria are based on four main clinical features, comprising:

1. spontaneous recurrent nosebleeds,
2. muco-cutaneous telangiectasia,
3. visceral involvement, and
4. an affected first degree relative.

These parameters define "definite HHT" where three criteria are present, "suspected HHT" with two criteria, most commonly family history and

Table 2. Curaçao criteria with the four main clinical symptoms

1. Epistaxis: spontaneous, recurrent nose bleeds
2. Multiple (muco-)cutaneous telangiectasia
3. Visceral lesions such as:
   - gastrointestinal telangiectasia (with or without bleeding)
   - pulmonary AVM (arteriovenous malformation)
   - hepatic AVM
   - cerebral AVM
4. Family history with an HHT-affected first degree relative

nosebleeds, or "unlikely HHT" with one criterion – for example, spontaneous nosebleeds without a family history, or a first degree relative of an HHT patient without any signs of the disease (Table 2).

Management and follow-up

Nose and skin

Diagnostic measures for nose and skin involvement are bases primarily on visual inspection. To enable a comparability of the severity of epistaxis with other studies, a standardize protocol was developed by Bergler et al. which helps to categorize the degree of epistaxis according to the frequency and intensity of bleeding (Bergler et al. 2002) Table 3.

Table 3. Intensity and frequency of epistaxis according to Bergler et al. (2002)

Intensity of bleeding	Frequency of bleeding
Grade I: slight stains on the handkerchief	Grade 1: less than once a week
Grade II: soaked handkerchief	Grade 2: a few times a week
Grade III: bowl or similar utensil necessary	Grade 3: more than once a day

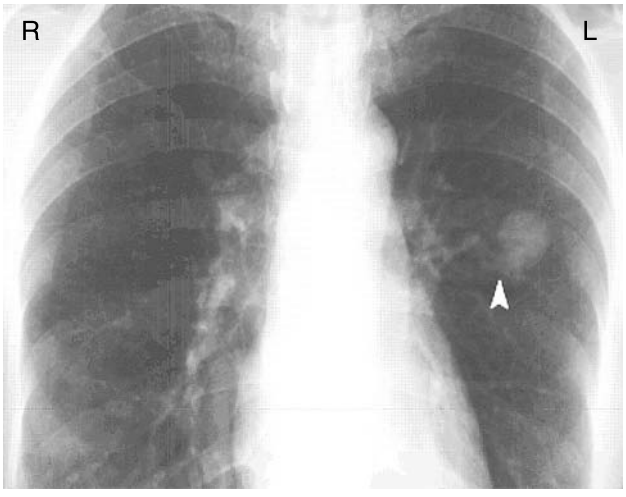

Fig. 7. Conventional chest X-ray showing a nodular lesion (arrow) in the upper lobe of the left lung.

Lungs

A screening examination for PAVMs is strictly recommended due to the severe complications which can arise from PAVMs such as stroke or brain abscess. Supine and erect pulse oximetry, conventional chest radiography (Fig. 7) as well as arterial-blood gas analyse serve as important screening method to detect individuals with suspected PAVMs (Haitjema et al. 1995, Sluiter-Eringa et al. 1969, Shovlin and Letarte 1999, Robin et al. 1976). However, many pulmonary arteriovenous malformations appear below the diaphragm because of their posterior location in the lung (Haitjema et al. 1995, Sluiter-Eringa et al. 1969), making chest X-ray not sufficient enough. Contrast echocardiography has the ability to detect intracardiac shunts and has shown to detect pulmonary AVM when pulse oximetry examination or even pulmonary angiographic findings are negative. Agitated saline, with its small air bubbles – also called micro-bubbles – is injected intravenously and creates visible contrast that can be observed in the left atrium on echocardiography. The presence of contrast in the left ventricle indicate right-left-shunts (Ueki et al. 1994, Shub et al. 1976). The presence of shunts detected by contrast echocardiography, can be verified by high-resolution helical computed tomography scanning with three-dimensional reconstructions

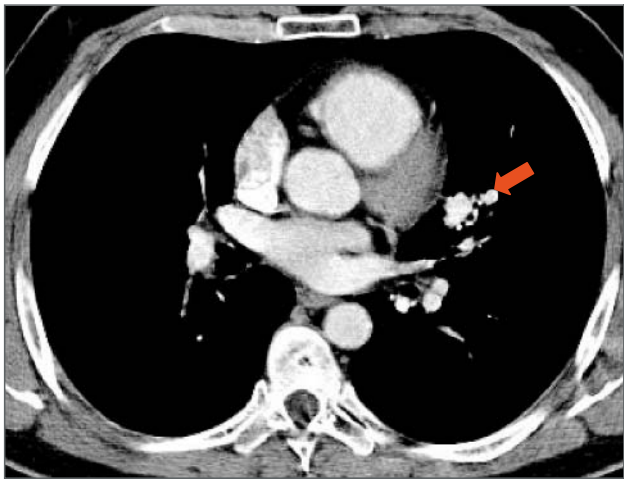

Fig. 8. Axial multi-slice CT scan after intravenous contrast confirms a hypervascularized pulmonary AVM in the left upper pulmonary lobe (⟶).

(Fig. 8). It conveniently identifies small, multiple lesions and effectively demonstrates the architecture of vessels in pulmonary arteriovenous malformations (Remy et al. 1994). Apart from the helical CT scan with contrast agent which also implicates an exposure to radiation and can be very cost-effective, pulmonary angiography has been advocated as an important screening method for pulmonary AVMs. It is required for therapeutic embolisation and is also mandatory to determine the position and structure of abnormal vascular lesions prior to surgical treatment. However, angiography is labour-, cost- and radiation-intensive, asks for a hand of an experienced radiologist and its use should be limited to individuals in whom non-invasive diagnostic tests strongly suggest the presence of PAVMs. According to recent studies, a prophylactic measure with antibiotics before any surgical intervention in HHT patients with known or assumed PAVMs is strongly recommended as complications arising from PAVM can be of septic event with severe cerebral involvement, such as brain abscess or hemiplegia due to a thrombembolic event (Kjeldsen et al. 1999).

Brain

For diagnostic screening purposes, cerebral magnetic resonance imaging (MRI) is currently the most sensitive non-invasive method, though it can also fail to detect the presence of AVMs. Though recommended, the question of whether asymptomatic HHT patients should be screened for cerebral AVM still remains controversially discussed (Easey et al. 2003).

GI-tract and liver

Telangiectasia occur throughout the GI-tract, and are more commonly situated in the stomach or duodenum, than in the colon. They are visualised by endoscopy and are similar in size and appearance to mucocutaneous telangiectasia, but may be surrounded by an anaemic halo. Arteriovenous malformations as well as aneurysms are less common (Reilly and Nostrant 1984). For possible liver involvement, ultrasound imaging as well as abdominal CT scan are in routine clinical use for detection of possible liver involvement.

Differential diagnosis

The clinical triad of telangiectases, recurrent epistaxis and inheritance is typical for patients with HHT. Possible differential diagnosis are idiopathic telangiectasia with occurrence at an older age or CRST (calcinosis, Raynaud phenomenon, sclerodermia, telangiectasia) syndrome. This syndrome, a variation of sclerodermia, is defined by cutaneous calcinosis, Raynaud phenomenon, hypomobility of the oesophagus, sclerodermia and telangiectasia. Antibodies against centromeric structures are typical for the syndrome (Maire et al. 1986).

Treatment

As curative treatments are not available for patients with HHT, all therapeutic effects remain symptomatic, or organ-directed.

Especially in the management of epistaxis with failure to medical treatment, a vast majority of different treatment options has been established, e.g. systemic hormone therapy, electrocautery, brachytherapy, embolisation or laser surgery using the Nd:YAG-, KTP- or CO_2 laser. In recent years, very encouraging and positive results could be gained with a new combined treatment approach consisting of "argon plasma coagulation" (APC) and topically applied estriol nose ointment (Bergler et al. 2002). In the treatment of skin lesions, the KTP laser has shown to be very effective.

Treatment of PAVM is based on the size, number and location of the lesions and the specific complications as well as the general condition of the patient. The therapy for symptomatic congenital PAVMs previously consisted of surgical resection entailing local excision, segmental resection, lobectomy or pneumonectomy. However nowadays, percutaneous transcatheter embolisation by coil or balloon is the treatment of choice in patients with PAVM (Fig. 9a–c) (Guttmacher et al. 1995, Kjeldsen et al. 1999).

Future diagnostic developments

The understanding of HHT is expanding rapidly. However, many multi-centred research studies are still

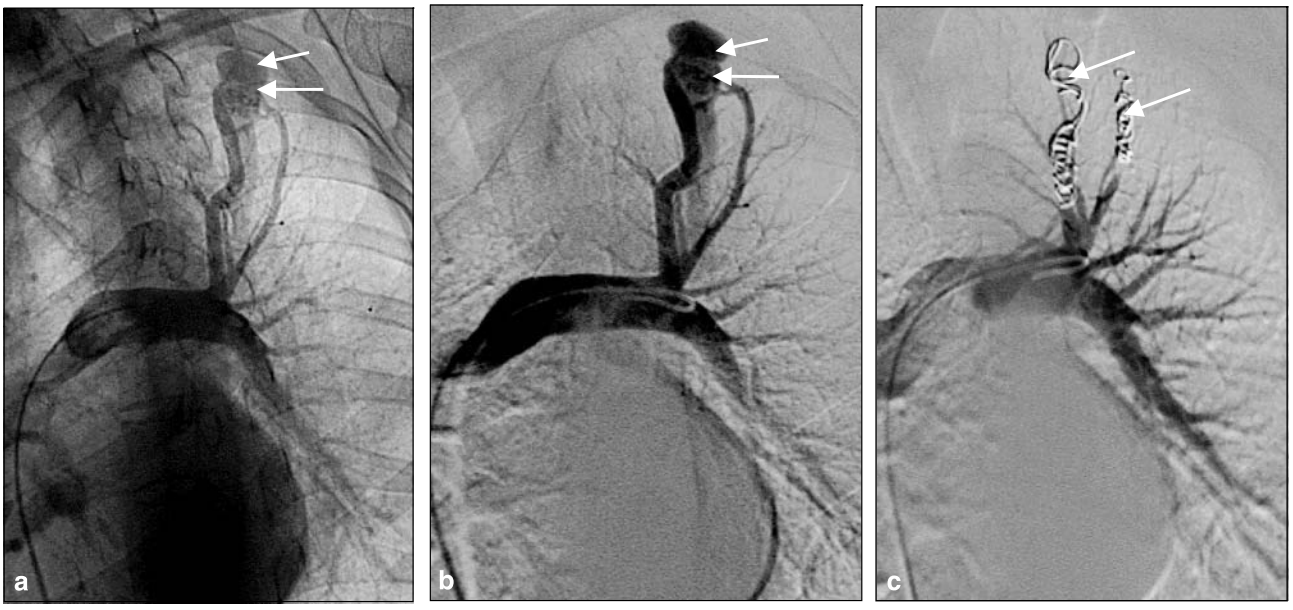

Fig. 9. (**a**–**c**) Pulmonary angiography confirms 2 AVMs arising from the upper segmental branches of the left pulmonary artery (⟶). Selective embolisation with platinum coils (**c**) results in successful occlusion of the pulmonary AVMs.

necessary to establish the needed correlations between genotype and phenotype. Currently, there are only a few specialised human genetic laboratory centres that offer diagnostic blood tests for HHT genotype identifications. However, these genetic tests are still very expensive and not in daily clinical use. At times, it is difficult to specify the genotype within members of the same family, as mutations within a family can vary immensely. Recently, different cytokines and pro-angiogenic factors such as the vascular endothelial growth factor (VEGF) have been identified, which have shown to be highly elevated in serum samples of HHT patients. These cytokines might serve as a potential plasma marker for HHT screening purposes (Sadick et al. 2005a,b). However, further studies are still necessary for a better understanding of HHT which may also bring critical insights into other diseases involving vascular damage and repair.

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