Hereditary haemorrhagic telangiectasia: state of the art

Telangectasia emorragica ereditaria: stato dell'arte

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Key words

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Parole chiave

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Summary

Hereditary haemorrhagic teleangiectasia (HHT) or Rendu-Osler-Weber disease is a genetic autosomal-dominant disorder characterised by the presence of vascular telangiectases in mucocutaneous tissues, visceral organs and the Central Nervous System. Pulmonary arteriovenous malformations have a variable incidence rate ranging between 15-33%, and the safest treatment is transcatheter embolotherapy. Haemmorrhages from the gastrointestinal tract occur in 10-40% of patients with HHT localized in duodenum and colon and can be treated with endoscopy and laser coagulation, but this procedure is not efficacious for vascular anomalies in small intestine since this site cannot be easily reached. The prevalence of cerebrovascular malformations in hereditary haemorrhagic telangiectasia patients is 5-27%, and there are several types described including telangiectasias, cavernous angiomas, arteriovenous malformations, and aneurysms. Cerebrovascular malformations can be treated by: neurovascular surgery, embolization, and stereotactic radiosurgery, but the appropriate course of action for dealing with asymptomatic cerebrovascular malformations is still debated. The most common symptom in HHT patients is epistaxis, which can sometimes be so profuse that it requires multiple transfusions and iron supplementation. Nose bleeds begin before 10 years of age and become more severe in later decades. A multitude of different treatments are available, tailored to the severity of epistaxis. These include: hormonal therapy with oestrogens, application of fibrine tissue sealant, laser coagulation, embolization and septal dermoplasty using Saunder's technique. Aim of this study is to review diagnostic and therapeutic techniques, since continuous growth and danger of these arteriovenous malformations require early diagnosis, adequate treatment, prolonged follow-up and screening of the family.

Riassunto

La Telangiectasia emorragica ereditaria o Malattia di Rendu-Osler-Weber è una patologia genetica autosomica-dominante caratterizzata da malformazioni vascolari dei tessuti muco-cutanei, viscerali e del Sistema Nervoso Centrale che possono essere causa di emorragie di varia entità. Le alterazioni vascolari a livello polmonare, con un'incidenza variabile del 15-33%, si manifestano come delle anastomosi arterovenose il cui trattamento di scelta è l'emboloterapia transcatetere. Emorragie si verificano anche nel distretto gastroenterico nel 10-40% dei pazienti con telangiectasia emorragica ereditaria. Le telangiectasie localizzate nel duodeno e nel colon possono essere trattate endoscopicamente mediante coagulazione laser, mentre tale procedura non è efficace per le anomalie vascolari del piccolo intestino poiché questa sede risulta difficile da raggiungere. Le malformazioni cerebrovascolari, presenti nel 5-27% dei casi, si manifestano sotto forma di telangiectasie, angiomi cavernosi, malformazioni arterovenose ed aneurismi. Il trattamento viene eseguito mediante chirurgia neurovascolare, embolizzazione e radiochirurgia stereotattica, ma è ancora dibattuta la reale necessità di intervento nelle forme asintomatiche. Il sintomo più comune nei pazienti con telangectasia emorragica ereditaria è l'epistassi, che può talvolta essere talmente profusa da richiedere trasfusioni multiple e somministrazione di ferro. Le emorragie nasali si manifestano in forma lieve già nell'infanzia, diventando più severe e frequenti nelle successive decadi di vita. Sulla base dell'entità del sanguinamento differenti possono essere le metodiche di trattamento, quali: la terapia ormonale con estrogeni, le applicazioni locali di colla di fibrina, la coagulazione laser, l'embolizzazione e la setto-dermoplastica secondo Saunders. Scopo del nostro lavoro è stato quello di fornire un'aggiornata revisione delle tecniche diagnostiche e terapeutiche, poiché a causa della continua crescita e della pericolosità di queste malformazioni arterovenose, è necessaria una precoce diagnosi, una adeguata terapia, un follow-up prolungato ed un eventuale screening dei familiari del paziente.

Introduction

Hereditary Haemorrhagic Teleangiectasia (HHT) is a rare systemic autosomal-dominant disorder of angiogenesis characterised by the presence of vascular telangiectases in mucocutaneous tissues, visceral organs, and the Central Nervous System (CNS).
Although Sutton described what is now known as HHT, in 1864, Rendu first recognized the combination of hereditary epistaxis and telangiectases in 1896 as a specific entity distinct from hemophilia. The following year the report appeared of Osler and Weber, whose names appear in the common eponym for this condition (Osler, Weber, Rendu disease). In 1909, Hanes coined the term "Hereditary Haemorrhagic Teleangiectasia" defining the disorder [1] and its features.

Genetics

According to the current literature, the prevalence of HHT is reported to be 1:3500 [2 3].
Although the disease occurs primarily in whites, cases have been reported in Asia [4], Arabia [5] and Africa [6].
This disorder has an autosomal dominant inheritance, and only patients with the heterozygous state survive. Penetrance of the gene has been estimated to be 97% [3].
Recent studies on HHT patients revealed a link between the presence of the disease and two genetic mutations, which occur on chromosomes 9 and 12, which have, therefore, been differentiated into a Type 1 and a Type 2 with different phenotypes [7 8].
The gene at chromosome 9q33-34 is called the endogline gene and it codes for an endothelial cell receptor protein which transforms growth factor-β. This factor is involved in regulating tissue repair and angiogenesis but it is not yet clear how this molecular defect leads to the formation of telangiectases, although it is believed that distruption of cell migration and adhesion may cause vascular dysplasia [1 9].
The mutation on chromosome 9 seems to occur in patients with HHT who have a high prevalence of pulmonary arteriovenous malformations (PAVMs) [10 11] and cerebral involvement [1 11 12].
The mutated gene (ALK-1) on chromosome 12 codes for the activin-like receptor kinase [7 8].
HHT has a variable expression and, therefore, organ involvement and severity vary between individuals in a same family.

Vascular Lesions

Arteriovenous malformations (AVMs) are not always present in patients with HHT, but they may occur in lungs, gastrointestinal (GI) tract and brain.

Pulmonary arteriovenous malformations (PAVMs) are direct, low-pressure, artery-to-vein connections that result in a direct right-to-left shunt. They have a variable incidence rate in patients with HHT (15-33%) [13] and 70% of patients with PAVMs have HHT [14 15]. Recent studies have demonstrated that patients with mutations in the 9q34 gene present a higher incidence of PAVMs than HHT patients with a chromosome 12 mutation [16].
Most PAVMs are localised in the lower lung (70%) and are usually supplied by the pulmonary artery and drain into the pulmonary vein [17]. Shunting of unoxygenated blood through these direct right to left shunts can lead to significant hypoxaemia, cyanosis and dyspnoea. Furthermore, since there is no capillary filter, small blood clots, bacteria, and, occasionally, air may pass directly through the PAVM into the systemic circulation, causing ischaemic events in various organs. In fact, a large number of patients with PAVMs suffer from episodes of cerebral ischaemia. The multiplicity of PAVMs increases the prevalence of cortical infarction, from 14% in patients with a single PAVM to 27% in those with multiple PAVMs. Cerebral abscesses have been presumably related to paradoxical embolization via PAVM [18].
In 1983, White et al. proposed a classification of PAVMs based on segmental pulmonary artery anatomy [19] where PAVMs were divided into simple and complex types. The simple type was defined as having a single segmental artery and draining vein, the complex type was defined as having two or more arteries supplying the PAVM and one or two draining veins. The aneurysm connecting the artery and vein was either a thin-walled sac without septation or a more complicated lesion with multiple interconnecting vascular channels. More recently, this classification has been modified, based on further observations and the report of Remy [20], and thus it is now estimated that approximately 10% of PAVMs are complex and 90% are simple.
Contrast Echocardiography (CE) is used in the screening of HHT patients with suspected PAVMs. It is a simple test in which a small amount of saline solution is agitated, creating "microbubbles", and injected into the vein. The bubbles go up through the arm and pass through the right chambers of the heart and into the blood vessels of the lung. In the pulmonary circulation, the microbubbles are detected with an ultrasound (US) transducer, placed on the chest wall. In individuals with a PAVM, the bubbles will pass through the PAVM and will appear in the left atrium and ventricle of the heart within 3-5 heartbeats of their appearance in the right-sided chambers. A positive CE indicates that a patient has PAVMs but does not give any information concerning the size, location, or number of PAVMs or whether treatment is recommended. High-resolution helical computed

tomography (CT) canning without the use of contrast medium is necessary to demonstrate the presence of PAVMs [21].

A complete diagnostic pulmonary angiogram with separate right and left injections should be obtained prior to embolotherapy.

In fact, the safest and most effective mode of treatment as far as concerns long-term results is transcatheter embolotherapy. Recurrences are easily retreated with good long-term results [22]. The most common means of embolization currently used is the detachable balloon. Coils are used in large sized arteries or aneurysms. Surgical resection of a solitary PAVM is also efficacious, but the advantages of transcatheter embolotherapy, including lower procedural morbidity, shorter hospital stay and rapid return to work, favour this technique [23]. Patients with PAVMs require long-term follow-up, every 5 years, to detect the growth of small PAVMs which may increase in size ultimately causing paradoxical embolization and stroke [1].

Haemorrhages from gastrointestinal telangiectases are often painless, and may thus go unrecognized until the patient becomes debilitated, has melena or anaemia.

It is estimated that the prevalence of blood loss, via telangiectases, in the gastrointestinal tract, occurs in 10-40% of patients with HHT, and with onset at a much later age than epistaxis (55 years *vs.* 11 years) [24 25]. The most frequent site of bleeding is in the upper GI tract, mainly in the stomach or duodenum, only 10% of patients have telangiectases in the colon.

Some studies have demonstrated that treatment with a low-dose combination of oestrogen and progesterone reduces the need for blood transfusion in patients with HHT. The mechanism of action of this hormonal treatment is unknown, but may be the result of inducing squamous metaplasia of the mucosa overlying the gut telangiectases.

Arteriovenous malformations located at the level of duodenum and colon can be treated with endoscopy and laser coagulation using neodymium: yttrium-aluminum-garnet (Nd:YAG) laser [26]. Unfortunately, the treatment of telangiectases in the small intestine with endoscopic laser or bipolar coagulation has not been successful since these GI lesions cannot be easily reached [27]. Some studies report the use of systemic low-dose enteral aminocaproic acid, but the effectiveness of this therapy has not yet been established [28 29].

The decision to use drug therapy in HHT should take into account the number of telangiectases, severity of bleeding and potential side-effects of treatment, in each individual patient [30].

Hepatic involvement in patients with HHT is relatively frequent. Arteriovenous shunts are of three types: arteriovenous, arterioportal and portovenous [31] and the vast majority of these are asymptomatic. The lack of symptoms is, in most cases, because the degree of shunting is well tolerated and compensated for by the heart. The presence of intra-hepatic shunting, while considerably altering the intra-hepatic vascular dynamics, does not lead to significant intrinsic liver disease, hence the synthetic function of the liver remains preserved. Symptoms, such as dyspnoea, fatigue and high output congestive heart failure, may be direct manifestations of an artery-to-vein shunt, or manifestations of portal hypertension, like splenomegaly, varices and enlarged portal vein. There is no general consensus on the benefit of liver screening in HHT patients, especially since the overwhelming majority of patients remain asymptomatic and there is no preventive therapy. Ianora et al. reported that CT may be better than US in the screening of HHT patients for liver involvement, since the multiphasic imaging may help not only in the detection, but also in the characterization, of the liver vascular malformations [32]. Unlike embolisation of AVMs in the lung or brain, hepatic embolisation is associated with significant morbidity and mortality often resulting in fatal hepatic necrosis [33]. Therefore, at the present time, even though some groups continue to practice hepatic artery embolotherapy, there is consensus among most experts that liver transplantation constitutes the definitive treatment for hepatic involvement [34].

The prevalence of *cerebrovascular malformations (CAVMs)* in HHT patients ranges from 5% to 27%, and there are several types described, including telangiectases, cavernous angiomas, AVMs, and aneurysms [35-37]. Common neurologic symptoms are migraine headaches and seizures caused by the "steal" of blood into the CAVM. Other symptoms include brain abscess, transient ischaemic attacks, stroke and subarachnoid haemorrhage [38]. The cause of these symptoms is unclear, but is not thought to be related to the presence of CAVMs since their prevalence is low and the prevalence of neurologic symptoms in HHT patients is high [39]. It seems that 61% of neurologic symptoms are related to the presence of PAVMs, because emboli pass through PAVMs and reach the cerebral circulation. Only 28% are caused by intra-cerebral haemorrhage from cerebral or spinal arterio-venous malformations [38]. Cerebral telangiectases and AVMs can be detected by standard Magnetic Resonance Imaging (MRI) [1 40], but Fulbright's preliminary experience with cerebral angiography demonstrated that most CVMs have an atypical appearance for vascular malformations on MRI, so the study can underestimate the prevalence of CVMs [41]. A few cases have been reported in the literature on the risk of Intracranial Hemorrhage (ICH) in neonates with a family history of HHT. These cases suggest that prenatal imaging, including MRI and

sonography, may assist in ruling out large internal AVMs or detecting vascular dysplasias in children. However, definitive diagnosis depends on genetic analysis [42].
CAVMs can be treated in several ways such as: neurovascular surgery, embolisation, and stereotactic radiosurgery using gamma rays, but the appropriate course of action for dealing with asymptomatic CVMs is still debated [43].

Telangiectases

Telangiectases can occur on the mucous membranes and on the skin in different sites of the body: lips, tongue, palate, fingers, face, conjunctiva, trunk, arms, nail beds, or a combination of these [1].
A typical telangiectasia has a diameter of 1-2 mm and is composed of dilated vessels directly connecting an artery to a vein. A fully developed telangiectasia has venules that are dilated, convoluted, and extend through the entire dermis. In addition, the arterioles have an excessive layer of smooth muscle showing elastic fibre deficiency, and they connect directly to dilated venules. The perivascular space surrounding the telangiectasia contains lymphocytes. Microscopic characteristics include defects in the endothelial junctions of the cells and an incomplete smooth-muscle cell layer surrounding the vessel [44].
The exact pathogenesis of bleeding is not clear, but has been attributed by some to the "fragile" nature of the vessels and the loss of contractile tissue [44]. Bleeding occurs at the top of telangiectases without extravasating into the surrounding tissues and, consequently, it seems that the epithelial tissue overlying the telangiectasia is responsible for causing bleeding. The nasal mucosa has a delicate pseudostratified, columnar respiratory epithelium and is frequently subjected to mechanical trauma, while the skin is made up of keratinized stratified squamous epithelium. This difference in tissue strength explains why epistaxis, caused by spontaneous bleeding from *telangiectases of the nasal mucosa*, is the most common manifestation in HHT patients. It may be so severe as to require multiple transfusions and oral or i.v. iron supplementation. Recurrent epistaxis can begin before 10 years of age [45] and by the age of 21 in most. Bleeding becomes more severe in later decades in about two thirds of affected patients [46 47]. A multitude of different treatment options are available, tailored to the severity of the patient's symptoms. They include: hormonal therapy with oestrogens, application of fibrin tissue sealant [48], laser coagulation, embolisation, and septal dermoplasty using Saunders' technique [49 50].

Oestrogen therapy

This therapy was first proposed in 1952 when it was observed that epistaxis in patients with HHT tended to improve during pregnancy and become worse in menopause [51]. Knowing that oestrogens induce an epithelial metaplasia by changing the ciliated columnar epithelium to squamous epithelium, Koch et al. were the first to apply oestrogens systemically in the treatment of patients with recurrent epistaxis in HHT disease [51]. Several studies stressed the possible severe side-effects using this therapy, including nausea, weight gain, uterine bleeding, increased risk of breast cancer, gynecomastia, loss of libido, thromboembolic diseases and myocardial infarction. A recent report demonstrated that within 6 months of topical oestriol application, the ultrastructure of the normal mucosa surface changed into a cobblestone pattern with patches of cilia and microvilli, indicating the initial process of epithelial metaplasia [52 53].
The Authors demonstrated the efficacy of using topical oestriol ointment to cause squamous metaplasia to the nasal mucosa, thus making the telangiectases, previously treated with argon plasma coagulation, less vulnerable to local trauma [53].

Laser therapy

Several lasers are used to photocoagulate telangiectases in the nasal cavity. These include the Nd-YAG laser, the potassium-titanyl-phosphate laser, and the argon laser [54 55]. The wavelengths of these lasers make them more selectively absorbed by the haemoglobin, which allows coagulation of the telangiectasia without causing serious damage to the vessel wall or the epithelium overlying the telangiectasia [56]. Indeed, several studies have demonstrated that Nd-YAG laser is successful in treating epistaxis, but unfortunately telangiectases often reappear, after time, and patients need to undergo repeat procedures [57-59].

Embolisation

Angiographic embolisation of branches of the internal maxillary artery (IMA) has been performed to control nasal blood circulation in HHT patients. The study conducted by Waever has shown that, in swine, unilateral IMA occlusion causes a sharp transient drop in nasal mucosa blood flow to a still viable level, but it always returned to baseline in 2 to 8 days, depending upon the level of IMA occlusion. Rapid revascularisation of the nose makes this treatment impractical. These results support the current practice of therapeutic distal IMA occlusion for the treatment of acute refractory posterior epistaxis, but suggest that "prophylactic" IMA occlusion is not helpful to protect against episodes of recurrent epistaxis [60 61].

Septal dermoplasty

Septal Dermoplasty was first described by Saunders [49 50], in 1958, to treat patients with severe epistaxis caused by HHT. The aim is to replace the fragile nasal mucosa with a sturdier split-thickness graft of keratinized stratified squamous epithelium obtained from the thigh.
This procedure has been shown to significantly reduce the frequency of epistaxis episodes among HHT patients for 1 to 2 years [55 62]. In some cases, epistaxis continues after septal dermoplasty due to regeneration of telangiectases within the skin graft and contraction of the graft [62 63]. The best way to deal with recurrent telangiectases within a graft is by using Nd:YAG laser, and, if necessary, a repeat septal dermoplasty can be performed.

Diagnosis

The clinical diagnosis is relatively simple in patients displaying the classical features of the disease: epistaxis, telangiectases and a family history. In most cases, instead, not all manifestations are present at the same time and a diagnosis established with just two of them could be inexact. Moreover, the significance of symptoms related to involvement of internal organs is often overlooked. Many times, in the past, diagnostic criteria have been modified. At present, diagnosis of HHT is clinically made on the basis of the Curaçao [64] criteria, established in June 1999 by the Scientific Advisory Board of the HHT Foundation International, Inc. More stringent than previous guidelines, these criteria are based on the presence of spontaneous and recurrent epistaxis, multiple telangiectases on lips, oral cavity, fingers and nose, visceral lesions and family history. Diagnosis of Hereditary Haemorrhagic Telangiectasia is definite if 3 criteria are present, possible or suspected if 2 criteria are present and unlikely if fewer than 2 criteria are present.

Conclusions

Hereditary Haemorrhagic Telangiectasia is a genetic disorder associated with small AVM (telangiectases) of the skin, nose and GI tract, and larger AVM of the brain, lung and liver. The most common symptom is nose bleeding, that is sometimes so severe as to require multiple transfusions and oral or i.v. iron supplementation, often inducing HHT patients to seek the advice of the otolaryngologist. Therefore, a more thorough knowledge of its features becomes necessary in order to recognize, diagnose and treat this disease. Although epistaxis is the manifestation most affecting the quality of life of these patients, overlooked PAVms and CAVMs could be equally dangerous because of the risk of a stroke. These factors suggest the need of a standardized diagnostic protocol based on an accurate personal and family history, as well as not only a physical examination to find telangiectases, but also screening for CAVMs and PAVMS. AVMs in the lung, brain, GI tract and nose are treatable. In some cases, the treatment needs to be repeated because AVM can continue to grow, then patients require careful and continuous monitoring throughout their life. Once an individual with AVM or telangiectases and most probably HHT is identified, the family should receive genetic counselling and screening.
Therapeutic advances, including gene replacement, may now be a realistic possibility to repair the endothelial cell damage.

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