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Hereditary hemorrhagic telangiectasia: An informative review

Neha Rajpurohit, Piyush Kumar Bharbey, M. Jatin, Khayati Moudgil

Abstract:

Inherited hemorrhagic telangiectasia (HHT or Osler–Weber–Rendu syndrome) is a hereditary condition characterized by malformations of multiple blood vessels (vascular dysplasia), which may lead to bleeding (hemorrhaging). Chronic nosebleeds are often the first warning, and malformations in various blood vessels can lead to abnormalities in the lungs, brain, spinal cord, and liver. There are a number of therapies available for various aspects of HHT to improve the quality of life and avoid life-threatening complications. Individuals with HHT have an almost average life expectancy. HHT is inherited as a dominant autosomal trait. We have done this review to enlighten the scientific fraternity about HHT. In this review, we have tried to explain about HHT and its related management.

Keywords:

Abnormalities, bleeding, blood vessels, hemorrhagic, life-threatening

Introduction

Osler–Weber–Rendu syndrome/disease (OWRD) is also known as inherited hemorrhagic telangiectasia (HHT). OWRD is a rare autosomal condition that affects the entire body's blood vessels and causes bleeding.[1,2] Various internal organs, skin, and oral mucosa are affected. Iron deficiency and subsequent anemia, due to persistent epistaxis or gastrointestinal (GI) bleeding, are often the complications of HHT. There are no agreed recommendations for the treatment of HHT, while the only supportive intervention for patients is to include iron supplements, transfusion of red cells, and direct care at the bleeding sites needed.

Hereditary HHT is characterized by the occurrence of numerous arteriovenous malformations (AVMs), which lack capillary involvement and result in direct connections between arteries and veins. Anomalous plasma concentrations of the transforming growth factor-beta (TGF-β) and vascular endothelial growth factor (VEGF) were observed in patients diagnosed with HHT. Small AVMs are called telangiectasias. In lips, tongue, ears, fingers, GI mucosa, and buccal and nasal areas, these telangiectasias are most evident. For HHT, lesions start as small, flat telangiectasias, with a few vessels radiating from one level.[3] The lesion scale is typically pinpoint to pinhead, and can occasionally be larger. The color appears rosy to red and occasionally purple.[4]

Causes

HHT is an autosomal dominant trait inherited. In certain cases, the disease arises spontaneously due to a natural genetic alteration that may be attributed to a new mutation. All individuals in the HHT-affected family would get the same mutation. The causative mutation is typically different in various families, however, with over 600 different mutations found within those four genes believed to be causing HHT. Human characteristics, such as the classic genetic disorders, are the result of the association between two copies of a gene for that disorder, one

Department of Pharmacy Practice, JSS College of Pharmacy, JSS Academy of Higher Education and Research, Ooty, Tamil Nadu, India

Address for correspondence:
Dr. Khayati Moudgil, Department of Pharmacy Practice, JSS College of Pharmacy, JSS Academy of Higher Education and Research, Ooty, Nilgiris, Tamil Nadu, India.
E-mail: khayatimoudgil@jssuni.edu.in

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obtained from the father and one from the mother. In dominant disorders, it takes only a single copy of the disease gene (received either from the mother or father) to cause the disease. The risk of transmitting the condition from the infected parent to the offspring with each pregnancy is 50%, regardless of the resulting child's gender. Four genes which cause HHT have been identified by researchers. At least one gene has yet to be identified, and maybe more. The gene that induces called as endoglin whereas the protein it produces known as encodes. Endoglin is found on the surface of the cells which line the blood vessels inside. Scientists assume that endoglin binds to the TGF-β. The blood vessels do not mature in endoglin-deficient mice, and vascular smooth muscle production is failing. Another gene that triggers HHT is kinase 1 (ACVRL1)-like activin receptor gene. People with mutations in this gene are also more vulnerable to liver AVMs and heightened heart pressure (pulmonary hypertension). BMPR9, a mutation in another gene that induces predominantly family pulmonary hypertension, is sometimes associated with HHT's vascular characteristics. A distinct form of HHT is an unusual combination of HHT and juvenile polyposis, a condition in which GI tract contains polyps. Mutations in SMAD4 result from this form of HHT.

The genes which trigger HHT all protein code involved in the TGF-β/bone morphogenic protein (BMP) super signaling family. This group of proteins assists in controlling many cellular functions such as cell survival, proliferation, and differentiation. With malfunctioning signaling, blood vessel cells cannot shape properly (angiogenesis), triggering HHT characteristics. This consists primarily of four major symptoms for epistaxis such as telangiectasia of traditional locations ears, fingers, oral cavities and cerebral AVMs.[5]

Epidemiology

Hereditary HHT affects approximately 1 out of every 5000 people in North America, but the most prominent pervasiveness is observed in the Netherlands Antilles and France districts of the Afro-Caribbean.[6,7] The subtype is equally different, with type 1 HHT being found more in North America and Europe and type 2 being more common in the Mediterranean region and South America. For either case, these tests might think nothing about the real pervasiveness about illness because the result is frequently ignored and a few patients may be asymptomatic. HHT shows an uneven penetration, and clinical signs between patients will fluctuate, even within families with known mutations.

In adolescence, patients can relate a history marked by epistaxis, which is occasionally clear during preadulthood. Smooth epistaxis or draining inclinations can be seen rising with age and telangiectasia after childhood, even in adulthood.

Clinical signs of draining become increasingly apparent at maturity, often after 40 years of age. Side effects from fatigue may be an inherent grumbling at GI dying presentation, seen in around 33% of patients. Patients with ACVRL1 changes may add more, while those with MADH4 changes can arise prior to youth with adolescent colonic polyps, however, at the beginning of colorectal malignant growth (at an average age of 28, a long time).[8] As a group, patients with HHT are likely to have a decreased future, but this is highly dependent on the extent of the disease. Patients with no signs of inward organs (e.g., hepatic, cerebral, or aspiratory AVMs) are relied on to have an ordinary or near-normal life expectancy because about 10% of patients may become disabled from vascular complications. In an enormous case–control analysis, 675 HHT patients were considered using age- and sex-coordinated solid controls using an important UK consideration database focused on the population. HHT patients were expected to suffer the ill effects of cerebral sore, headache, ischemic/embolic stroke, cardiovascular collapse, colon malignant development, and the disease's hallmark of numerous draining intricacies. The contrasted risk proportion of death for HHT patients and controls was 2.03. In a single study, future was 7 years shorter in HHT patients, with two mortality tops: one under 50 years and one between 60 and 79 years. Finally, a population concentrate in Denmark demonstrated mortality rates double those of all those under the age of 60.[9]

Clinical Description

HHT shows age-related penetration that usually progresses with increased manifestations during lifespan. The average age at which AVMs grow and/or present symptomatically is very typical for specific organ. The disease with respect to the smaller dermis and mucosal lesions is typically most frequently progressive.

Examples include the following:

- About 50% of the diagnosed individuals report experiencing nose bleeding by age 10 and 80%–90% by age 21. Ultimately, persistent epistaxis hits as many as 95%[10]
- The percentage of individuals with side, face, and oral cavity telangiectasias is similar to the percentage of those with epistaxis, but the age at which apparent telangiectasias begin is typically 5–30 years older[11]
- Cerebral AVMs are primarily congenital, and secondary intracranial AVM has been identified as a symptom of HHT in infants and HHT babies.[12]

Epistaxis

Nasal bleeding is the most common characteristic, in which HHT patients seek medical attention. The average starting age is around 12 but varies from childhood to adulthood.

While nosebleeds are often involuntary, they also occur more frequently in patients with HHT secondary to severe trauma to the nose. In affected adults, the incidence of nosebleeds ranges from once a year to once a day.[13] The severity of the nosebleed ranges from a few drops of bright red blood that accumulates to gushing within the nose. Most affected individuals have only mild, occasional nosebleeds that rarely need medical treatment, and it can be difficult to cause bleeding in the nose while taking drug history or family history. Many of those with HHT, whose nosebleeds are initially on the moderate end of the spectrum when asked about recurrent nosebleeds, initially respond "no," thinking recurrent mild nosebleeds are normal. Epistaxis leads to chronic anemia and transfusion dependency in a minority of patients.

Telangiectasia

Although large proportions (95%) of the affected individuals eventually undergo facial, oral cavity, or hand telangiectasias, the average identification age is typically later than that of epistaxis but may be in childhood.[14,15] Thirty percent of the affected individuals report that telangiectasias first emerged before age 20 and two-thirds before age 40. Nevertheless, the most affected individuals, after close inspection, have multiple telangiectasias at characteristic locations throughout the first decade of existence. The amount of identified telangiectasias in the affected individuals, even far into adulthood, is still only 5–15, and can be very small. HHT telangiectasias are rarely diffuse, and often not very dramatic, except in some older patients. Adults without HHT can accumulate cutaneous telangiectasias as they age, especially in areas that are exposed to sunlight. Chronic liver disease telangiectasias are of the form "spider," with outward radiating central core, and small vessels. The majority of telangiectasias in HHT, in comparison, are punctuated or macular. Telangiectasias can be found anywhere in the GI but most especially in the stomach and the small intestine proximal. The images are displayed in Figure 1.

Gastrointestinal Bleeding

Approximately one-quarter of all adults with HHT inevitably suffer from GI bleeding, and the accountable telangiectasia is mainly found in the upper GI tract. Bleeding from GI telangiectasia most typically begins after age 50, is generally slow but constant, and sometimes gets more serious with age.[12] No particular foods or habits in HHT patients were identified as contributors to GI bleeding.

Central Nervous System

Cerebral AVMs occur in around 10% of the individuals affected. The risk of cerebral hemorrhage from these high-flow lesions is usually considered requiring treatment even for individuals of asymptomatic young age.[16]

The most common central nervous system (CNS) risks in patients with HHT, brain abscess, and ischemic stroke are, in general, secondary to right to left shunting associated with pulmonary arterial venous malformations (PAVMs).

Spinal arteriovenous malformations (AVMs) are often less common than brain AVMs, and are typically associated with symptoms of paralysis and/or back pain. Most are diagnosed and treated within the first decade of life.[17]

Hepatic Manifestation

In one study, the prevalence of hepatic vascular complications was 74%, and in another study, it was 41% using ultrasound inspection which regularly imaged the liver of the affected individuals using computed tomography (CT) scan. However, only a small minority is symptomatic (8% in the sample using CT).[18] Hepatic focal nodular hyperplasia occurs in HHT at prevalence greater than the general population, and the radiological imaging may raise questions about a hepatic tumor. Regardless of the hemorrhage risk, the needle biopsy of the liver is contraindicated in HHT, recognizing that focal nodular hyperplasia is a much more likely diagnosis than cancer can help guide treatment. It is shown in Figure 1.

Prognosis

Generally speaking, the future gives the impression of being abbreviated by OWRD (i.e., HHT); with proper screening and strong administration, the future may shift toward that of the ordinary population for most patients. Mortality indicates a peak early at age 50 and a peak later at age 60–79, associated with serious confusions.[19] Specifically on the level of foundational inclusion, especially aspiratory, hepatic, and CNS involvement, the anticipation is exceptionally subject to the seriousness of the sickness. Just 10% of patients suck the HHT intricacy dust. The commonness of brain AVM in HHT1 patients is 1000-overlap higher than the prevalence in all (10 out of every 100,000), and it is

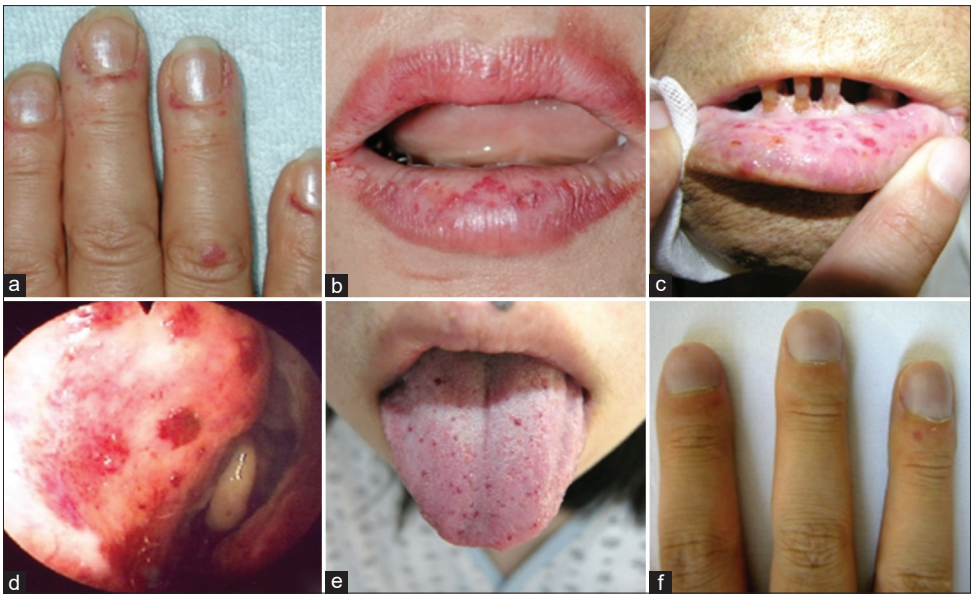

Figure 1: (a) Telangiectasia on the periungual region of the fingers, (b) telangiectasia on the lips, (c) telangiectasia on the oral mucosa, (d) bleeding in the plexus, (e) microtelangia on the tongue, (f) clubbing fingers with one small hemangioma

100-overlay higher in HHT2 patients.[20] Arteriovenous aneurysms of the pulmonary and CNS can show up further down the road.[21] Patients with aspiratory AVMs and GI tract telangiectasias are in danger of damaging lung discharge and GI tract forever. Various draining destinations may remember places for the kidney, spleen, bladder, liver, meninges, and mind. Strokes may either be hemorrhagic, or ischemic. Of patients with aspiratory AVMs, 2% of patients are diagnosed as having a stroke each year, and 1% of patients are diagnosed each year to develop a sore mind. Very infrequently, retinal arteriovenous aneurysms occur. Additionally, patients are at risk for high-yield heart fraud, headaches, and more sequelae. Visit nosebleeds and melena in the nose and GI tract can be the product of telangiectasia. Patients with an extreme form of HHT experience excessive drainage and associated iron-lack weakness. Intermittent epistaxis is seen in the same number of patients as 90%. The epistaxis tends to be increasingly true with age down the middle of the patients, and blood transfusions are needed in 10%–30% of patients.[20]

Management

Organ or tissue-specific therapy

Gastrointestinal tract

Therapy is futile because intense iron therapy is ineffective in maintaining hemoglobin concentration within reasonable range.[21] Fecal ritual blood tests are unspecific, as epistaxis-swallowed blood gives a positive result.

- Push enteroscopy, endoscopy, mesenteric and celiac angiography, and radionuclide testing can be used to assess the cause and extent of bleeding[22]
- Local treatment is based on endoscopic application of a fan, bicap, or laser probe.
- In identified cases, hormonal therapy with estrogen–progesterone and bevacizumab has lowered the transfusion requirements
- Small bowel bleeding sites and greater vascular malformations can be removed surgically after they have been detected in nuclear medicine studies.

Pulmonary arteriovenous malformations

Any PAVM with a feeding artery >1–3 mm detected by chest CT should be considered for the diagnosis of transcatheter embolization. PAVM treatment is recommended for dyspnea, exercise resistance, and hypoxemia, but is particularly essential for the prevention of lung hemorrhage and neurological complications of brain abscess and stroke, including in those asymptomatic in terms of pulmonary function and oxygen saturation. PAVMs are associated with migraine headaches in HHT patients, which often increase or decrease significantly after embolization.[23] Long-term follow-up by chest CT is suggested after transcatheter occlusion of PAVM due to reported re-canalization and development or growth of untreated PAVMs. In general, 6–12 months postocclusion follow-up CT is performed, and if no reperfusion of treated AVM (s) or new PAVM (s) is detected, follow-up CT is typically administered at intervals of 5 years later.

Cerebral arteriovenous malformations

Cerebral AVMs with a diameter of >1.0 cm are usually treated with neurovascular surgery, embolotherapy, and/or stereotactic radio-operation.[24]

Hepatic involvement

Liver biopsy should be prevented in people with HHT. Treatment of cardiac insufficiency or renal dysfunction alongside renal vein malformations is often troublesome. In fact, signs are not associated with the apparent severity of the vascular abnormalities found on CT scanning. The embolization of hepatic AVMs, which was successful in the treatment of PAVMs, led to extreme hepatic infarctions. Many patients with symptomatic hepatic involvement with intense medical therapy may be satisfactorily treated to relieve hepatocyte dysfunction and cardiac insufficiency. For those individuals (usually older ones) whose symptoms did not respond to medical care, liver transplantation became the preferred treatment.[25]

Pharmacological therapy

Because surgical procedures available for some forms of HHT can be temporary or ineffective (e.g., ablation of GI telangiectasias), require significant morbidity (liver transplant and nasal septal dermoplasty), or are reversible (nasal laser coagulation), patients with HHT have long-awaited safe and reliable drug therapies. Oral or intranasal topical estrogens may be beneficial, but women are limited to long-term therapy.

Raloxifene will make the genes ENG and ACVRL1 more expressive.[26] Recent reports of small series and cases showed therapeutic benefits from anti-angiogenic drugs such as bevacizumab and thalidomide, and antifibrinolytic drug – tranexamic acid, particularly for treating severe GI bleeding, epistaxis, and symptomatic hepatic vascular malformations. Many such agents in randomized trials are underway.

HHT diagnosis requires a multidisciplinary approach involving professionals from various fields such as cardiology; hepatology; radiology; head, nose, throat (ENT); genetics; and hematology. This analysis is based primarily on the HHT biology.

Bevacizumab, a recombinant humanized monoclonal antibody that inhibits angiogenesis by inhibiting VEGF, is an intravenous drug used to minimize the incidence and intensity of epistaxis and helps enhance the quality of life.

Discussion

The first and the most common sign is chronic nose bleeding and malformations of various blood vessels, which may result in abnormalities by affecting various organs such as brain, spinal cord, lungs, and liver. Few treatments are available to improve the quality of life in patients with HHT, thus also preventing life-threatening complications in individuals. Patients with HHT have a near-normal life expectancy. Paleness in an HHT patient could be available because of bleeding from the existing vascular deformities. In certain patients, because of unreasonable nose bleed, there could be the ingestion of a modest quantity of blood. This can imitate an upper GI bleeding with indications of melena and hematemesis. The treatment of HHT is chiefly moderate. Tragically, there is no changeless solution for bleeding and iron deficiency in these patients. The treatment rotates around the counteraction and intense administration of these signs, including blood transfusions and iron supplementation. New treatments such as hormonal, thalidomide, and bevacizumab have demonstrated promising outcomes, yet further assessment is required for their continuous use.

Conclusion

Hereditary HHT is an acquired problem, defined by various vein deformities (vascular dysplasia). Constant nosebleeds are often the main symptom, and the distortion of different veins can lead to deviations from the norm that affect the lungs, cerebrum, spinal cord, and liver. An array of medicines exists to boost personal satisfaction for the various highlights of HHT. HHT is acquired as an attribute which prevails autosomal. HHT dedication was promoted with the obvious proof of a few disease-causing characteristics, but the board of both symptomatic and asymptomatic individuals remains profoundly challenging for seasoned pros. Danger dialog and nuanced inquiries of the threat advantage should be delicately and adequately discussed for age, family, social, and national foundations. Major clinical and testing challenges remain impossible that we can predict and avoid possible disease anymore closely in a situation in which most people would have no noticeable inconvenience.

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Conflicts of interest

There are no conflicts of interest.

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