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Diagnosis and Treatment of Hereditary Hemorrhagic Telangiectasia

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Background: Hereditary hemorrhagic telangiectasia (HHT) is a rare genetic disorder known for its debilitating symptoms. More than 90% of patients with HHT experience epistaxis, and they average up to 18 bleeds per month. We review the current literature on the pathophysiology, clinical presentation, and management of HHT.

Methods: We searched MEDLINE, EMBASE, and PubMed and identified 19 articles published since 2000 with current information on HHT.

Results: HHT is a disease more commonly associated with significant morbidity rather than mortality. The morbidity of the disease and decreased quality of life are the result of the recurrent and potentially severe epistaxis that the majority of patients with HHT experience. During active epistaxis, the effective emergency techniques of locally applied pressure, nasal packing anteriorly and/or posteriorly, and cauterization are effective. Medical treatment with antiestrogen therapy has shown promising results, but further research is needed to determine the long-term side effects and the limitations of lifelong therapy. Research directed toward bleeding reduction and prevention has yet to have a breakthrough. Although initial reports suggest that intranasal bevacizumab is an effective agent, further research is required.

Conclusion: Interventional treatments in life-threatening and/or severe circumstances will continue to be used because of their effectiveness. Research into the pathophysiology of HHT has led to the development of potential therapies that prevent and decrease the severity of epistaxis, but the current evidence is insufficient to ascertain best practice. At present, appropriate management of acute epistaxis coupled with early diagnosis and referral to an ear, nose, and throat specialist should be the mainstay of treatment.

Keywords: *Arteriovenous malformations, epistaxis, genetic diseases–inborn, telangiectasia–hereditary hemorrhagic*

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INTRODUCTION

Hereditary hemorrhagic telangiectasia (HHT) is a genetic disorder characterized by the primarily dominant autosomal hereditary transmission of dermal, mucosal, and visceral telangiectasias and visceral arteriovenous malformations (AVMs). The disorder was initially documented as Osler-Weber-Rendu disease, named after the clinicians who first described the condition: Rendu in 1896, Osler in 1901, and Weber in 1907.[1-3] In 1909, Hanes gave the disorder its current name based on its clinical characteristics. Documentation of the disease's prevalence varies. Two countrywide studies in Denmark determined a prevalence of 15.6 per 100,000, while a study in France reported an incidence of 11.9 per 100,000.[4,5]

In this article, we review the current literature on the pathophysiology, clinical presentation, and management of HHT.

METHODS

We searched MEDLINE, EMBASE, and PubMed using the search terms hereditary hemorrhagic telangiectasia *and* treatment *or* investigation *or* management. Additional search limits were a publication date after the year 2000 and articles in the English language. We initially identified 170 titles in PubMed, 144 in MEDLINE, and 240 in EMBASE. We excluded titles that did not address HHT epistaxis, management, or treatment; duplicate titles; and titles specified as case reports. In total, we reviewed 42 abstracts and further excluded articles for irrelevance, small case series, and industry-run trials. We then reviewed the full text of 19 articles and checked the reference lists for further relevant articles, including articles published prior to 2000.

PATHOPHYSIOLOGY OF HEREDITARY HEMORRHAGIC TELANGIECTASIA

Because the direction in treatment of HHT has moved to a focus on prevention rather than symptomatic treatment, understanding the genetic mechanism behind the disease and the gene mutations is important for appreciating the pharmacology of preventive agents. Gene coding mutations are responsible for HHT, with 3 genes accounting for 85% of

clinical cases: (1) HHT type 1 mutation of ENG coding for endoglin, (2) HHT type 2 mutation of ACVRL1 coding for activin receptor-like kinase (ALK), and (3) the combined disorder of juvenile polyposis/HHT mutation in MADH4 that codes for transcription factor SMAD4.[6-8] These predominant gene mutations are involved in the encoded proteins that mediate transforming growth factor beta superfamily signaling, initially thought to be central to the disease's pathogenesis.[9] Various hypotheses for the pathogenesis of HHT have subsequently been proposed, with the predominant conclusion being an impairment of blood vessel formation and/or an imbalance in multiple proangiogenic and antiangiogenic factors.[9,10]

A study using enzyme-linked immunosorbent assay to compare vascular endothelial growth factor (VEGF) levels in 47 control patients compared to 41 patients with HTT found a statistically significant increase in VEGF levels in the HHT cohort.[11] The significance of this finding was supported by research that found that ALK receptors, resulting from ACVRL1 coding in HHT, regulate VEGF expression, the factor important in angiogenesis.[12]

CLINICAL PRESENTATION AND DIAGNOSIS OF HEREDITARY HEMORRHAGIC TELANGIECTASIA

The genetic mutations resulting in impairment of blood vessel development form the basis of the clinical features of telangiectasias and visceral AVMs. Mucous telangiectasia lesions are most often found in the oral and nasal cavities and on the lips, fingers, and nose. The lesions of the nasal cavity, especially of the nasal septum, are responsible for epistaxis, the primary symptom of HHT. Aassar et al looked specifically at epistaxis in patients with HHT and found that 93% of patients experienced epistaxis.[13] The average age of onset was 12 years, and patients averaged 18 bleeds per month. This predominant feature of the disease causes a high level of morbidity for many patients, with 18% documenting epistaxis so severe that it impeded their ability to work and pursue normal activities. The pulmonary, gastrointestinal, liver, cerebral, and spinal AVMs can cause a range of life-threatening complications, but AVMs are far less common than epistaxis.[14-16]

For diagnosis of HHT, the widely accepted standard is the Curaçao criteria, based on the most characteristic features of disease: (1) spontaneous and recurrent epistaxis, (2) family history, (3) cutaneo-mucous telangiectasia, and (4) visceral lesions.[17] A definitive diagnosis of HHT is made if a patient exhibits at least 3 of the 4 criteria. In 2009, an HHT guidelines working group developed recommendations for screening and testing once a diagnosis of HHT has been made.[18] The working group recommendations include using the Curaçao criteria as the basis of diagnosis and as an indication for subsequent genetic testing to confirm the diagnosis. The working group also stated that patients who meet 1-2 criteria may also be suitable for genetic testing. The recommended initial genetic testing is for the 2 most prevalent mutations: ENG and ACVRL1. If negative results are returned, testing of SMAD4 should be considered. If the diagnosis is proven or assumed, the rest of the screening involves investigation of common disease features: magnetic resonance imaging for cerebral vascular malformations, transthoracic contrast echocardiography with agitated saline for pulmonary AVMs, Doppler ultrasound in patients with abnormal liver function for liver vascular malformations, and annual hemoglobin results for all patients.[18]

TREATMENT OF HEREDITARY HEMORRHAGIC TELANGIECTASIA

During active epistaxis episodes, patients with HHT are aided by locally applied pressure, nasal packing anteriorly and/or posteriorly, and cauterization.[19,20] These techniques are especially effective in anterior bleeds associated with the Kiesselbach plexus, but ongoing severe posterior bleeds may need surgical intervention. Research shows that endovascular treatment is an effective technique in situations of life-threatening epistaxis.[19] While simple aids may be effective, because of the frequency of 18 epistaxis episodes per month that Aassar et al reported, these common aids can expose patients to risks, including damage to healthy nasal mucosa from recurrent cauterization and the infection risks associated with nasal packing.[13]

Research into the molecular biology of the disorder has helped produce management options for preventive approaches to decrease the number of epistaxis episodes as well as their severity.[9] These approaches vary from simple practices and common medications to surgical interventions to medication that targets specific VEGF receptors.[21]

Using humidifiers and applying moisturizers to the nasal mucosa have been reported to reduce the severity of bleeding, and the HHT guidelines working group recommends these practices.[19,20]

Furthermore, promising results have been reported for some medical treatments. Antiestrogen trials have demonstrated good outcomes, with consecutive studies evaluating the benefit of tamoxifen 20 mg/day in patients with HHT.[22,23] Both studies were undertaken in Israel, where an initial group of 21 patients with HHT was enrolled in a double-blind, placebo-controlled clinical trial in which 10 patients were treated with tamoxifen and 11 were treated with placebo.[22] The patients were evaluated at 6 months, and the group taking tamoxifen reported a statistically significant decrease in the severity of bleeding. The results were quantified via examination of the amount of telangiectasia and the patients' opinions on severity rather than on a measurable scale. These 21 patients continued into a cohort trial with an additional 25 patients to evaluate the long-term effects of treatment.[23] All the patients were treated with tamoxifen 20 mg/day and completed follow-up with evaluation of their hemoglobin levels; completion of the Rhinosinusitis Disability Index; and recorded bleeding time, frequency of bleeding, and number of transfusions during the previous month. The mean duration of follow-up was 23 months, at which time the investigators found statistically decreased mean bleeding times and increased hemoglobin levels compared to the patients' pretreatment values. Eight patients were lost to follow-up for various reasons. Importantly, 3 patients did not improve on the treatment, and 1 female patient had ultrasound-diagnosed uterine mucosal hypertrophy that resolved with treatment cessation. Nevertheless, the study showed clear statistical improvement in symptoms compared to initially documented symptoms, and no other patients were reported to have side effects from the treatment. This use of tamoxifen,

however, requires further trials with long-term follow-up to appropriately investigate the use of this treatment for a lifelong disease.

Another medical treatment trialed systemically is the commonly used hemostatic agent tranexamic acid. Patients taking tranexamic acid at a dose of 3 g/day had decreased durations of average daily bleeding compared to patients taking placebo.[24] However, tranexamic acid had no effect on patient hemoglobin level, the primary study outcome, and many patients in the tranexamic acid treatment group reported common side effects such as vertigo and diarrhea. Although the authors reported that these side effects were tolerated, side effects can have a detrimental effect on compliance. Furthermore, the power of this study was limited by its small sample size, with only 20 patients evaluated.[24]

Focusing more on prevention, many interventional and surgical therapies have been trialed with differing outcomes. Recent research has involved comparison of new therapies including laser photocoagulation, electrosurgical plasma coagulation, and sclerotherapy. To assess outcomes, these studies used the Epistaxis Severity Score (ESS), a standard tool used to quantify the severity of epistaxis in patients with HHT.[25] In 2014, Luk et al compared the more commonly used laser photocoagulation to electrosurgical plasma coagulation (EPC); however, the study size was small (6 and 5 patients, respectively) and although the EPC group had a reduction in ESS scores, the difference did not reach statistical significance.[26] A study by Boyer et al evaluated the use of sclerotherapy with sodium tetradecyl sulfate (STS) compared to standard treatment of moisturization, packing, and coblation.[27] ESS decreased in the patient group receiving sclerotherapy and STS, but with the small study size, the difference did not reach statistical significance. The Boyer et al study was also limited by its lack of randomization and blinding. Its main strength lies in the researcher's prior studies that reported patient tolerability of the treatment and a low side effect profile, limited though by short observation.[27,28]

A study into the surgical methods of septodermoplasty and laser ablation found that while these interventions were effective in the short term, they had no long-term positive effect as epistaxis inevitably recurred in patients with HHT.[29]

Cutaneous microvascular free flaps and Young's procedure have been trialed. The former involves removing nasal mucosa and resurfacing the nasal passage using a skin flap, while the latter involves suturing mucocutaneous flaps to surgically close the nostril. Pau et al have noted that although case studies have reported good outcomes with free flaps, large-series clinical trials are needed so the effectiveness of free flaps as a treatment option can be quantified.[30] Young's procedure has been trialed in severe transfusion-dependent patients.[31] Forty-three patients had the procedure performed at 3 international HHT centers: 38 patients received bilateral nasal closure, and 5 patients received unilateral nasal closure. Postoperative follow-up was achieved on 36 patients, with 100% reporting subjective improvement and 30 patients (83%) reporting complete cessation of epistaxis after the procedure. Patients reported the well-documented side effects of decreased taste, xerostomia, and anosmia, but all patients reported they would rather tolerate these side effects than ongoing epistaxis.[31]

After the discovery that ALK receptors regulate VEGF expression, the factor important in angiogenesis, new treatments were designed to act on these receptors. Bevacizumab (Avastin), a VEGF inhibitor, is used as an intravenous injection, intranasal spray, and submucosal injection. Karnezis et al reported statistically significant improvements in ESS after use of injected intranasal bevacizumab 100 mg in a trial of 19 patients during a 9-month period.[21] Their results showed that intranasal topical injection suited patients with initially low ESS. Conversely, 6 patients who had high ESS after the initial injection benefitted from 8 subsequent topical doses of bevacizumab of 100 mg. The authors concluded that the topical therapy clearly contributed to the patients' decreased ESS at follow-up.[21]

The side effect profile of bevacizumab has been a topic of investigation. A prior trial of systemic bevacizumab used to treat hepatic vascular malformations and high cardiac output reported 89 adverse events in 21 of 25 participants.[32] The ELLIPSE study followed to evaluate whether localized nasal spray therapy with bevacizumab had the same systemic effects.[33] The ELLIPSE investigators determined that no systemic uptake of bevacizumab occurred, and they reported none of the prior systemic side effects.

While that study was able to clarify systemic side effects, in a study of 52 patients—21 receiving topical bevacizumab and 31 receiving a submucosal injection of bevacizumab—Chen et al acknowledged that 5 patients who had been treated with both submucosal bevacizumab and the potassium titanyl phosphate laser along the bilateral cartilaginous septum had inhibited local mucosal healing that resulted in septal perforation. The researchers changed the protocol so that the cartilaginous septum was not lasered or injected, and once this treatment change was made, no patients developed this side effect during the mean follow-up period of 12 months.[34]

While these initial trials showed positive outcomes, a follow-up to the ELLIPSE study did not. A randomized clinical trial evaluating the use of topical bevacizumab in patients with HHT measured the duration of bleeding for 3 months in 3 groups of patients receiving different doses of bevacizumab and a fourth group receiving placebo.[35] With an initial cohort of 80 patients and follow-up from 75 participants, the placebo group had the lowest bleeding time at the 3-month mark, and the trial was terminated.[35] While the results of this trial are concerning regarding the effectiveness of topical bevacizumab, prior findings suggest good results from this therapy with minimal side effects. Additionally, this follow-up study did not evaluate the effectiveness of injectable administration, so whether more effective administration forms are possible is not currently known.

Overall, a number of methods—ranging from practices such as humidification to medications such as antiestrogen and tranexamic acid to interventional procedures—have been researched. However, many of these studies were limited by small study populations, lack of blinding, and failure to reach statistical significance. Therefore, current evidence is insufficient to ascertain best practice for prevention and treatment of epistaxis in HHT.

CONCLUSION

HHT is a disease more commonly associated with significant morbidity rather than mortality. The morbidity of the disease and decreased quality of life are the result of the recurrent and potentially severe epistaxis a majority of patients with HHT experience. During active epistaxis, the effective emergency techniques of locally applied pressure, nasal packing anteriorly and/or posteriorly, and cauterization will likely remain paramount. Medical treatment with antiestrogen therapy has shown promising results in trials from Israel, but further research is needed to determine the long-term side effects and the limitations of lifelong therapy. Research directed toward bleeding reduction and prevention has yet to have a breakthrough. Although initial reports suggest that intranasal bevacizumab is an effective agent, with some studies resulting in decreased ESS and manageable side effects, further research is required with longer treatment periods and follow-up. In the meantime, appropriate management of acute epistaxis coupled with early diagnosis and referral to an ear, nose, and throat specialist should be the mainstay of treatment.

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