Hereditary haemorrhagic telangiectasia*

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Abstract

Background: Hereditary haemorrhagic telangiectasia is an autosomal dominant vascular disease characterized by recurrent epistaxis, mucocutaneous telangiectasia and visceral arteriovenous malformations.

Methodology: The genetic basis and pathophysiology of the disease are discussed. Diagnostic criteria and the clinical course of the condition are considered. The current management options, both medical and surgical, are reviewed.

Conclusions: Hereditary haemorrhagic telangiectasia requires specialist treatment for the problems it causes, and is best managed in specialist centres. Epistaxis is often the major symptom, significantly affecting patients' quality of life. An understanding of the available treatment options is therefore important for the otorhinolaryngologist.

Key words: hereditary hemorrhagic telangiectasia, Osler-Weber-Rendu syndrome, epistaxis, arteriovenous malformations, therapeutic

Introduction

Hereditary haemorrhagic telangiectasia (HHT), also know as Osler-Weber-Rendu syndrome, is a genetic vascular disease with autosomal dominant inheritance [(1)]. It has a prevalence of 1 in 5,000 – 9,000 but with some geographical variation [(2, 3)]. It is characterized by recurrent epistaxis, mucocutaneous telangiectasia and visceral arteriovenous malformations (AVMs), which may be found in the lung, liver, brain or gastrointestinal tract. It has also been associated with a prothrombotic state due to elevated factor VIII [(4)], and possible intrinsic immune dysfunction with higher rates of severe infections [(5-7)]. There have been conflicting reports of different rates of common cancers as well as improved cancer survival in patients with HHT [(8, 9)].

Hereditary haemorrhagic telangiectasia is caused by a single mutation in one of three known genes. Over 80% of HHT is due to mutations in the ENG gene on chromosome 9, which encodes for the protein endoglin, or the ACVRL1 gene (chromosome 12), which codes for activin receptor-like kinase 1 (ALK1) [(10, 11)]. Over 700 different mutations have already been identified in these two genes, which cause HHT1 and HHT2 respectively (see http://hhtmutation.org). ENG mutations tend to be slightly more common than ACVRL1 in northern Europe and North America, while the reverse is true in the Mediterranean, although reports vary [(1, 12, 13)]. A juvenile polyposis/HHT overlap syndrome (JPHT) accounts for approximately 2% of HHT; this is due to mutations in the MADH4 gene on chromosome 18, which codes for the SMAD4 protein [(12, 14)]. Two further gene loci have been identified recently, the HHT 3 gene on chromosome 5 and HHT4 on chromosome 7 [(15)]. Currently, mutations are not found in 20% of families [(1)].

The proteins encoded by these genes all mediate signalling in the transforming growth factor-β (TGF-β) superfamily pathway, which regulates a diverse array of cellular functions including angiogenesis [(15-17)]. Haploinsufficiency of these proteins causes dysfunction of circulating angiogenic cells and an imbalance in angiogenesis [(16-18)]. High plasma levels of TGF-β and vascular endothelial growth factor (VEGF) have been found in patients with HHT [(19, 20)], but the angiogenic response is disorganized and results in the development of abnormal vascular structures with fragile walls and turbulent blood flow [(21)]. These findings have

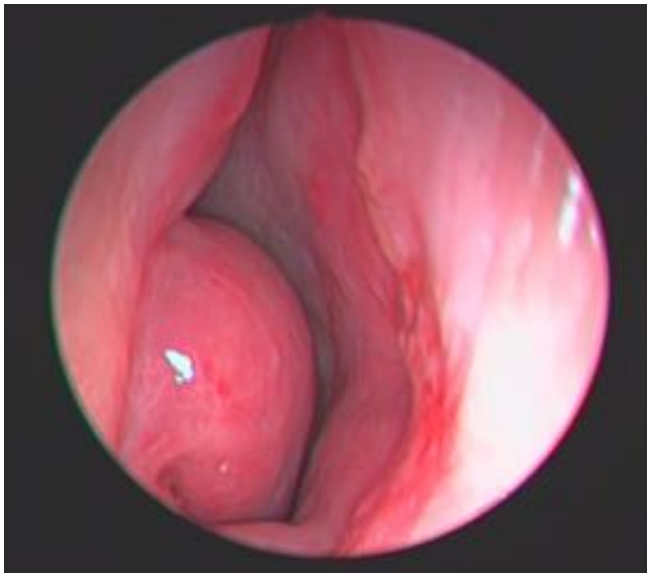

Figure 1. Nasal mucosal telangiectasia.

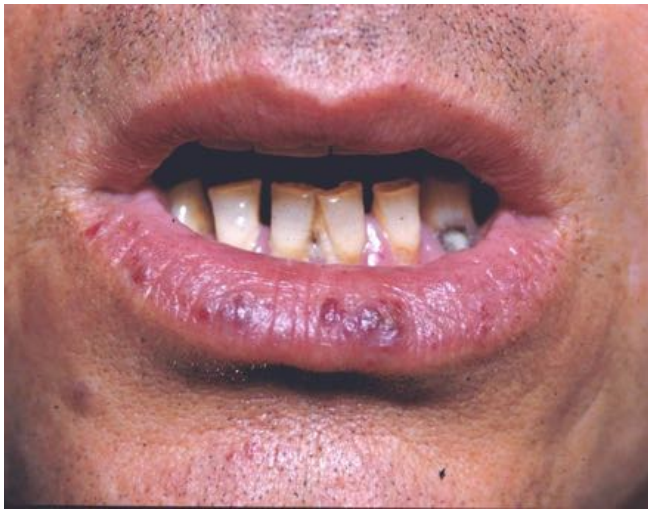

Figure 2. Mucocutaneous telangiectasia.

led to the use of antiangiogenic drugs in the treatment of HHT.

There is a genotype-phenotype relationship in HHT, with pulmonary and cerebral AVMs more common in HHT1 and hepatic AVMS in HHT2 [22], but symptoms and disease progression vary even between family members with the same genetic mutation [23]. Symptoms also change during the course of a patient's life; over 85% have reported that epistaxis worsens with age [24].

Discussion

Diagnosis

There are evidence-informed consensus guidelines regarding the diagnosis and management of HHT and the prevention of HHT-related complications [25]. The clinical diagnosis of HHT is based on the consensus diagnostic Curaçao criteria (Table 1); a diagnosis is "definite" if three criteria are present, "possible" or "suspected" if two are present, and "unlikely" with fewer than two [26]. However, HHT should be considered as "possible" with any family history, until proven otherwise by genetic testing [1]. Genetic testing is not required if a definite clinical diagnosis has been made, but it allows screening of asymptomatic family members or those with a possible diagnosis [23].

Once a diagnosis has been made (or is suspected as "possible"), specialist referral should be made and screening for asymptomatic AVMs should be arranged as per the consensus guidelines [25].

Table 1. The Curaçao criteria for the clinical diagnosis of hereditary haemorrhagic telangiectasia (HHT)[26]; AVM = arteriovenous malformation.

Criteria	Definition
Epistaxis	Spontaneous, recurrent
Telangiectases	Multiple, at characteristic sites: lips, oral cavity, fingers, nose
Visceral lesions	Gastrointestinal telangiectasia; pulmonary, hepatic, cerebral or spinal AVMs
Family history	First-degree relative with HHT according to these criteria

Clinical features

Hereditary haemorrhagic telangiectasia is rarely symptomatic in childhood, but 70% of patients will have symptoms by the age of 16, and over 90% by 40 years [27]. However, symptoms have been reported to start as late as 70 years [24]. Epistaxis is the most common symptom, occurring in over 90% of patients [13, 28, 29]. It varies in severity and frequency but can significantly affect patients' quality of life [30-33]. Certain foods, often those containing high salicylate levels, have been reported to worsen epistaxis, as have low humidity and changes in temperature [34]. Various subjective grading systems are available [35, 36], and objective classification of the pattern of lesions has also been described [37]. Nasal telangiectasia are tortuous dilated superficial vessels (Figure 1), very sensitive to even the minor trauma of airflow, and a lack of elastin fibres means that they do not vasoconstrict to limit bleeding [38].

Mucocutaneous telangiectasia occur in approximately 80% of patients (Figure 2), typically increasing from the third decade [1]. Whilst the lip, tongue and buccal lesions may bleed, cutaneous lesions are usually only cosmetically troublesome.

Pulmonary AVMs (PAVMs) occur in 15 – 50% of patients with HHT, but up to 85% of those with HHT1 [39-41]. Whilst sporadic PAVMs do occur, 90% of all PAVMs occur in the context of HHT so an incidental finding should prompt screening for HHT [42]. PAVMs are abnormal direct communications between the pulmonary arterial and venous circulations, bypassing the capillary bed between the pulmonary and systemic circulations [43]. The subsequent lack of filtration allows paradoxical embolism with an increased risk of ischaemic stroke, reported in 10 – 36% of untreated patients, and cerebral abscess, reported in 8-19% [44]. Right to left shunting of deoxygenated blood may cause hypoxaemia and dyspnoea, with significant effects on quality of life [40]. The fragile vessels may also rupture causing potentially life-threatening haemoptysis or haematemesis, the risk of which is increased in pregnancy [45]. Migraines are twice as common in patients with HHT compared to the normal population, particularly in those with PAVMs, and tend to improve with treatment of the PAVM, suggesting an aetiological role [24, 46]. Most PAVMs are asymptomatic so screening is recommended to allow treatment and prevention of complications [25]. The gold standard screening method is with transthoracic contrast echocardiography, which has a sensitivity of 93% [42]; if this is positive then formal computed tomography (CT) is performed to plan treatment, although CT alone is used in some units [43, 44]. Percutaneous embolotherapy is the treatment of choice, with excellent success rates [44, 47, 48]. Reperfusion is reported in up to 20% so long-term follow-up with CT scanning is required, initially after six months then every 3-5 years [25, 48]. Prophylactic antibiotics are recommended with any dental or surgical procedure and patients are advised not to scuba dive, even after treatment [25].

Cerebral vascular malformations (CVMs) occur in approximately 10-20% of HHT1 and 1% of HHT patients, compared to 0.01% of the general population [25, 49, 50]. They may be arteriovenous fistulae (AVFs), small AVMs, micro AVMs, cavernous malformations and capillary telangiectasias [25, 50, 51]. Only one-third of neurological complications in HHT are related to CVMs; the remainder are secondary to paradoxical embolism due to PAVMs [51]. The spontaneous haemorrhage rate is 1-4% per year; it has been reported to be lower in HHT patients (0.5% per year) but this is controversial [50, 52]. AVMs tend to be small and superficial, but AVFs are almost exclusively found in young children with a cumulative risk of intracranial haemorrhage of nearly 100% [51]. Screening is recommended in both adults and children but remains controversial [25], as both the morbidity and mortality rates for treatment are 6.5% [51]. Diagnosis is with magnetic resonance imaging (MRI), but treatment planning requires angiography. Treatment may be with embolization, surgery or stereotactic radiotherapy, and should be carried out at specialist centres [53].

Hepatic AVMs (HAVMs) occur in 32-84% of HHT patients, being more common in HHT2, but are only symptomatic in approximately 8% of cases [13, 25, 54-56]. The most common complications are high output cardiac failure, portal hypertension and biliary necrosis [55]. Screening, with Doppler ultrasound (US), is not recommended unless patients are symptomatic or have elevated liver function tests [25, 56]. Treatment is symptomatic, with liver transplant the only definitive cure [54]. However, the anti-VEGF drug bevacizumab (Avastin, Genentech Inc, San Francisco, CA, USA) has recently been used with some success in severe cases [57, 58].

Gastrointestinal telangiectasia are found in up to 80% of HHT patients [13, 25], but bleeding only occurs in 15-30% of cases, usually from the 5th or 6th decade [1, 25, 26]. Endoscopy is therefore only recommended in patients with overt bleeding or chronic anaemia that cannot be explained by the degree of their epistaxis [23, 25]. The exception to this is patients with JPHT, who require regular upper and lower surveillance endoscopy because of the risk of malignancy [1].

Pregnancy in HHT

All pregnancies in women with HHT should be considered high-risk from an obstetric point of view, because of the increase in HHT-related complications that are known to occur. Large series have shown a 1% risk of major haemorrhage from PAVMs, a 1.2% stroke rate and 1% maternal mortality [45]. Complications are much lower if screening and treatment for visceral AVMs has been carried out prior to pregnancy [45, 59]. While there is no evidence to support pre-pregnancy MRI screening for spinal AVMs, which occur in approximately 1%, it is often asked for by anaesthetists prior to epidural insertion [45, 59].

Management of epistaxis

Acute epistaxis

Avoid packing if possible, as it only traumatises the mucosa with further bleeding on pack removal. If acute haemorrhage is severe and persistent, then an absorbable material such as gelatine sponge, Surgicel™ (Ethicon, Wokingham, Berks, UK) or Nasopore™ (Polyganics, Groningen, The Netherlands) soaked in adrenaline or tranexamic acid may be helpful [27]. Commercial gelatin matrix products (Floseal™, Baxter, Newbury, Berks, UK; and Surgiflo™, Ethicon, Wokingham, Berks, UK) have recently been used to treat acute epistaxis, avoiding formal nasal packing and admission in small numbers of patients [60,61]. Some patients may self-administer such absorbable packing to avoid hospital attendance. A variety of newer, less traumatic non-absorbable packs are now available, such as RapidRhino™ (Arthrocare UK Ltd, Knaresborough, North Yorkshire, UK), some of which may also be self-administered, If bleeding persists despite these measures, a longer term pack soaked in Whitehead's

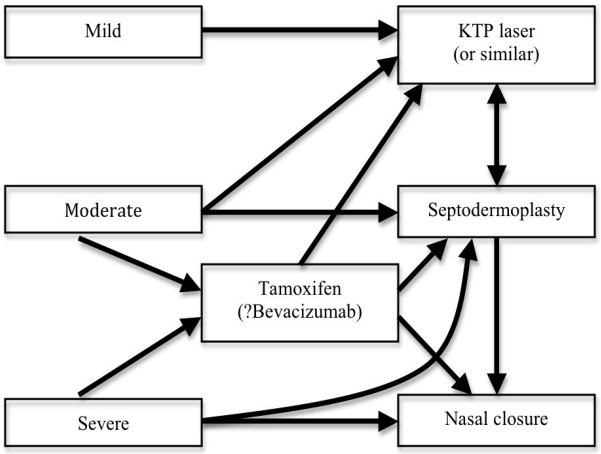

Figure 3. A suggested treatment algorithm for HHT-related epistaxis.

varnish may be required [62]. Whilst there is a historical lack of safety data regarding Whitehead's varnish, the senior author has used it in the nose and sinuses for many years without problem; manufacturing issues have unfortunately limited its availability in recent years [63].

Rarely packing may need to be combined with embolization or arterial ligation, prior to consideration of more definitive treatment such as nasal closure. Whilst potentially helpful in the short-term, there is no evidence that either of these latter interventions have any long-term benefit due to the 'end-organ' nature of the disease and re-establishment of collateral supply. [64, 65]. Furthermore it is rarely technically possible to undertake local arterial ligation without precipitation of significant bleeding. Thus, embolisation is preferred in the acute life-threatening situation if other strategies fail. Contraindications to embolisation include "dangerous" anastomoses between the internal and external carotid arteries, bleeding from the anterior or posterior ethmoid arteries, and severe atheromatous disease [64]. The risk of stroke, albeit small, should be discussed and may deter patients from undergoing treatment.

Silver nitrate nasal cautery should be avoided in both acute and elective management of HHT-related epistaxis as it causes full-thickness mucosal damage, which increases the risk of septal perforation that can hinder further treatment in these patients. It has also been suggested to stimulate neoangiogenesis with regrowth of telangiectasia [27].

Chronic epistaxis

Apart from bilateral nasal closure, treatment only aims to reduce the frequency and severity of bleeding rather than stop it completely. Treatment algorithms have been proposed [62, 66], based on the severity of bleeding, but patient choice is also important; our suggested treatment algorithm is shown in Figure 3. Chronically low haemoglobin levels may require regular oral iron supplementation; some patients undergo regular iron transfusions. Blood transfusions may be required intermittently for symptomatic anaemia. Despite their bleeding tendency, HHT patients should still be treated with antiplatelet or anticoagulant agents if there is a strong indication for their use, such as an acute coronary syndrome or cardiac stenting [25, 67].

Medical treatment

Topical treatment

Some patients find lubricants helpful in reducing crusting, but their application may trigger epistaxis. A sesame oil/rose geranium oil compound has been reported to significantly improve symptoms in 75% of patients [68]. Intranasal tranexamic acid, caustic soda, snake venom coagulation and radiotherapy have all been used in the past with little evidence of benefit [69, 70].

Beta-blockers

Following on from its success in treating superficial haemangiomas in children, topical timolol has been reported to improve epistaxis [71, 72]. Whilst the exact mechanism is unknown, it is thought to be related to immediate vasoconstriction with later endothelial cell apoptosis and decreased VEGF expression [73]. Care must be taken to monitor heart rate and blood pressure even with topical beta-blocker use, as some patients are slow metabolizers due to genetically-determined enzyme function [72].

Antioxidants

Oral N-acetyl cysteine, an antioxidant, led to a reduction in frequency and severity of epistaxis in a non-controlled study, more so in patients with HHT1 than HHT2 [74].

Antifibrinolytic agents

Antifibrinolytics such as tranexamic acid have been used systemically as well as topically. A small randomised placebo-controlled double-blind trial showed a significant reduction in epistaxis over six months as measured by patient-reported epistaxis scores [75]. In vitro cultures suggest that tranexamic acid acts by stimulating the TGF-β /ALK1/endoglin pathway. Whilst there may be some short-term benefit from such medications, the longer-term risks of a procoagulant state must be considered in HHT patients given the recent evidence for increased factor VIII levels [4].

Hormonal treatment

Oestrogen cream has been shown to flatten prominent nasal telangiectasia and induce squamous metaplasia of the nasal mucosa (making it more resistant to trauma) within six months,

without elevation of serum oestriol levels [76]. Randomized controlled trials of oral oestrogen have shown benefit in transfusion-dependent patients [65]. However, the high doses necessary cause feminizing side effects that many men find unacceptable, and concern remains regarding its prothrombotic effects, particularly in view of the pro-coagulant state now recognised to exist in HHT [4]. Medroxyprogesterone has been used with some success and less feminization in older men [69]. The oral contraceptive pill and hormone replacement therapy may reduce bleeding in pre- and post-menopausal women respectively.

Tamoxifen is a more acceptable hormonal therapy for reducing HHT-related epistaxis. A double-blind placebo-controlled trial of this anti-oestrogen drug led to a significant reduction in the frequency and severity of epistaxis, with associated significant improvement in haemoglobin levels and quality of life, over an average follow-up period of two years [77]. Raloxifene is a selective oestradiol receptor modulator (SERM) of the same family as tamoxifen, licensed for osteoporosis in post-menopausal women. A prospective non-controlled study showed a significant reduction in the frequency and severity of epistaxis over six months, with no side effects [73]. In vitro experiments have shown that it increases expression of endoglin and ALK1 at the endothelial cell surface, potentially overcoming the insufficiency caused by HHT gene mutations [73]. Treatment with both drugs has been associated with an increased rate of venous thromboembolism [78]; HHT patients with a history of venous thromboembolism or ischaemic heart disease are advised against the use of these drugs.

Antiangiogenic therapy

Hereditary haemorrhagic telangiectasia has been shown to be associated with elevated serum and tissue levels of vascular endothelial growth factor (VEGF), a key factor in the control of angiogenesis [20]. VEGF leads to increased endothelial cell proliferation and neoangiogenesis, and is therefore a potential therapeutic target in HHT [79]. Bevazicimab is a humanized recombinant monoclonal antibody against VEGF, previously used in macular degeneration and certain metastatic cancers. There is one phase II study and multiple case reports or small series reporting on its systemic use in patients with HHT [57, 58, 79, 80]. It leads to a clinical improvement in epistaxis, gastrointestinal bleeding and both iron and transfusion requirements in most cases, and improved cardiac index and pulmonary hypertension in patients with high output cardiac failure secondary to HAVMs [57]. However, its side effect profile includes spontaneous gastrointestinal perforation, cytopaenia, hypertension, delayed wound healing, septal perforation, weakness and haemorrhage, concerns about which have understandably limited its use for epistaxis alone; it is also expensive and long-term maintenance treatment is required as its effect is not permanent [58, 79]. To try and mitigate these side effects, it has also been used intranasally, both as submucosal injections and in spray form [81-90]. Whilst most authors report reasonable efficacy with no/minimal side effects, there have been concerns regarding the development of septal perforations following submucosal injection [81, 83]. Most authors therefore advise against injecting bevacizumab over the cartilaginous septum [81, 83, 84, 86]. The optimum dose and route of administration have not yet been found, although extended systemic dosing intervals (three- to four-weekly) and very low dose systemic bevacizumab have been suggested [91, 92].

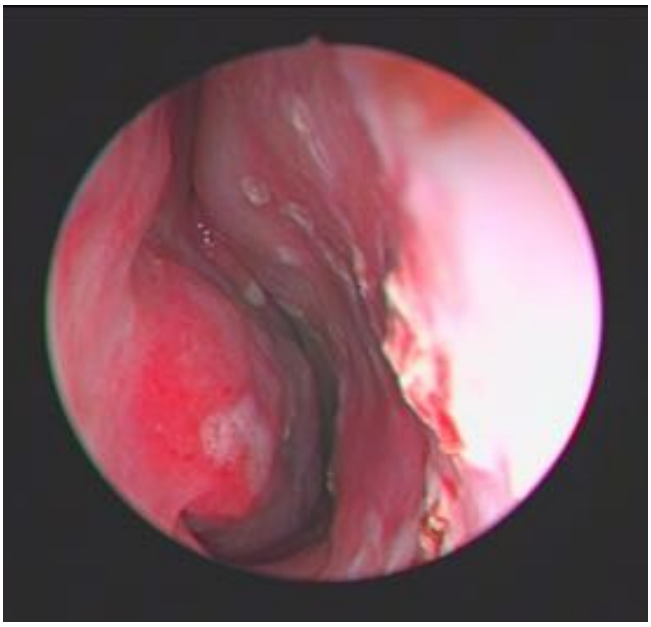

Figure 4. Nasal telangiectasia following KTP laser.

Thalidomide is also antiangiogenic, perhaps by inducing vessel maturation via platelet-derived growth factor signalling [93], and some response has been found in HHT-related epistaxis [94].

Surgical treatment

Endonasal laser coagulation

The potassium titanyl phosphate (KTP) laser is perhaps most commonly used, but argon, neodymium:yttrium aluminium garnet (Nd:YAG) and the pulse dye laser have all been employed successfully [95]. The argon laser has a wavelength of 488/514nm, and the KTP wavelength is 532nm; these are preferentially absorbed by the colour red, so are able to coagulate the individual telangiectasia without full-thickness mucosal injury (Figure 4) [96, 97]. The Nd:YAG laser causes significantly more tissue destruction than argon or KTP and the CO_2 laser is much less helpful with a higher risk of bleeding as it is a 'cutting' rather than 'coagulating' laser. The reduction in epistaxis severity and frequency after laser are not permanent, as new lesions will inevitably form, but it can be repeated ad infinitum if it is successful. Laser treatment tends to be most successful in patients who report mild to mo-

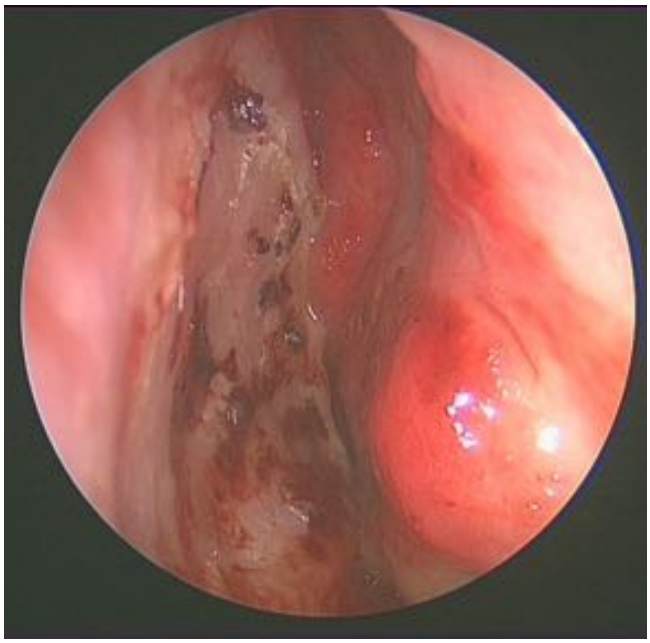

Figure 5. Previous septodermoplasty with shrinkage of graft and new telangiectasia seen anterior to graft.

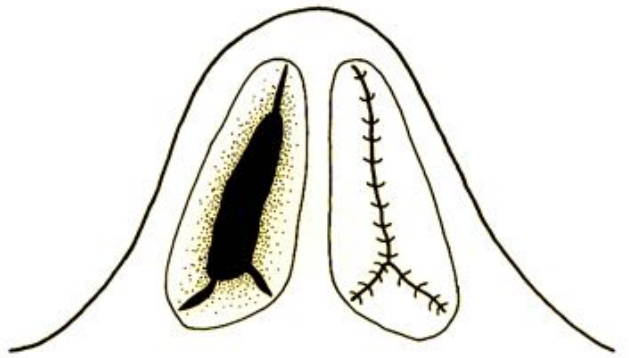

Figure 6. Incisions for nasal closure [69].

derate epistaxis, and repeated treatments may have an additive effect [96].

Other "local" surgical treatments

Argon plasma coagulation has been successfully used in a series of 52 patients, with 94% reporting a significant reduction in bleeding frequency and severity [76]. Coblation (electrosurgical plasma coagulation) has been shown to be safe and effective, and was recently reported to have similar efficacy to laser in a small group of patients [98, 99]. Submucosal bipolar radiofrequency causes submucosal sclerosis with preservation of the overlying mucosa, and a small pilot study showed a significant reduction in HHT-related epistaxis when applied to the nasal septum [100]. Submucosal injection of various sclerosants directly into septal and lateral nasal wall lesions has also been used with some success [28, 38, 101], under both local and general anaesthesia. However, visual loss has been reported after fibrin glue injections for HHT, so care must be taken and high pressure injections avoided [101].

Septodermoplasty

Septodermoplasty (SDP) was initially described by Saunders in 1959, the principle being to replace the anterior septal mucosa with a split-thickness skin graft (SSG) [102]. Saunders described a simultaneous bilateral procedure, but it is more commonly performed unilaterally today, to reduce the risk of septal perforation; the contralateral side can be grafted after two to three months [103]. A SSG is commonly used but other graft materials, including amniotic membrane, buccal mucosa and inferior turbinate mucosa, have been described [62]. In a group of 131 patients treated surgically for HHT, SDP led to a 57% reduction in the need for subsequent laser treatment over a five-year period [97]. The graft contracts over time; telangiectasia tend to reappear around it but do not seem to grow through it (Figure 5).

Nasal closure

Originally described by Young as a treatment for atrophic rhinitis [104], a modified technique was described by Lund in 1997 (Figure 6) [69]. This procedure tends to be reserved for (and requested by) those patients with severe epistaxis, unresponsive to other treatments, with significant reduction in their quality of life and overall wellbeing. By preventing nasal airflow the lesions are protected and do not bleed. A retrospective review of 43 patients who underwent nasal closure over six years reported complete cessation of bleeding where complete closure was achieved [105]. Patients may experience a dry mouth as a result of this procedure and the resultant obligate mouth breathing, and occasionally oral or lingual lesions will bleed more than previously because of the increased airflow. Interestingly, if the procedure is reversed, nasal telangiectasia are still present and bleeding starts again [69, 106].

Conclusions

Patients with HHT require a multidisciplinary approach to the multisystem problems it causes, and are best managed in specialist centres. Otolaryngologists play a prominent role because epistaxis is usually the major symptom, affecting quality of life and general well-being. An understanding of the available treat-

ment options is vital in the management of these patients.

Authorship contribution

JR: literature review and writing paper

VL: senior review and editing paper

Conflict of interest

None to declare

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