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Natural history and control of epistaxis in a group of German patients with Rendu-Osler-Weber disease*

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SUMMARY

***Introduction**: Epistaxis is the most common symptom of a complex, genetically determined vasculopathy, which is known under the notion hereditary hemorrhagic telangiectasia (HHT, Rendu-Osler-Weber-syndrome). This study was initiated to gain more knowledge about the natural history of epistaxis in a German HHT-population.*

***Patients and methods**: Data of 49 HHT patients were ascertained by interviewing these patients with a standardized disease specific questionnaire. Patients´ files were retrospectively reviewed for data concerning age, gender, past medical history, laboratory parameters, number of hospital admissions for epistaxis, conservative and operative types of therapy, treatment results and follow-up.*

***Main result**: Epistaxis was the first and most prominent symptom in 93% of the patients and could be triggered most frequently by stress. Half of the patients had experienced first episodes of epistaxis in childhood, but usually epistaxis did not become troublesome before the age of 35 years. The effects of hormonal changes or therapies with systemic hormones were inconclusive with regard to impact on epistaxis. Patients with septal perforations had to be admitted for inpatient epistaxis treatment more frequently than patients with an intact nasal septum. An overall reduction of frequency and intensity of epistaxis could be achieved in 89% of the patients through the daily use of nasal lubricants and a minimum of two treatment sessions with the Nd:YAG laser. However in none of the cases the treatment results were permanent. More than 50% of the patients, who had been screened for visceral arteriovenous malformations, were positive for pathologic vascular lesions.*

***Principal conclusion**: The natural history of epistaxis in German HHT patients is similar to previously described entities from other parts of the world. First clinical signs of HHT may be present at an earlier age than previously thought.*

Key words: epistaxis, natural history, hereditary hemorrhagic telangiectasia, Nd:YAG laser, septodermoplasty

INTRODUCTION

In the general population epistaxis is a common, but usually singular event [1]. Individuals with recurrent epistaxis on the other hand are likely to suffer from hereditary hemorrhagic telangiectasia (HHT, Rendu-Osler-Weber syndrome). HHT is inherited in an autosomal-dominant trait and is a disease of the entire vascular system. Affected individuals are likely to develop telangiectases, arteriovenous malformations (AVM) and aneurysms at various locations of the body [2]. Nosebleeds occur in 80 - 98% of all individuals with HHT [3] and they are a nuisance because of their recurrent nature. For most HHT patients epistaxis is more than an inconvenience, because it disturbs almost all aspects of life and often leads to secondary health problems like iron deficiency anemia, shortness of breath and malaise. A multitude of different treatment options have been developed for control of epistaxis in HHT; most of them offering rather palliation than cure. So far there is no generally accepted uniform treatment concept for epistaxis in HHT, which may be explained by the fact, that HHT is regarded as a rare disease and conclusions have so far been drawn from experiences with limited numbers of patients. Until recently, the German otolaryngologic literature focussed primarily on the treatment of epistaxis in HHT, spending little attention to the natural history of this prominent symptom. In order to gain more information on the natural history of epistaxis in German HHT patients and to evaluate our own treat-

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ment concept we have analysed a series of 49 consecutive HHT patients.

PATIENTS AND METHODS

In a retrospective study the data of 49 persons with the putative diagnosis of hereditary hemorrhagic telangiectasia (HHT) were reviewed. The respective persons had been patients of the Department of Otolaryngology of the University of Marburg in the time span from April 1998 to July 2003 because of recurrent epistaxis. Follow-up on an average was 28 months (minimum follow-up: 8 months, maximum follow-up: 60 months, standard deviation: 12.4). Prior to inclusion into the survey the diagnosis of HHT had been confirmed according to the clinical diagnostic criteria of the Scientific Advisory Board of the HHT Foundation International, so-called "Curaçao-criteria" [4]. The patients' files were reviewed for age, gender, medical history, family history, concomitant diagnoses, history of epistaxis, epistaxis therapy, treatment results, complications and follow-up. Interviews with the patients were conducted with a standardized questionnaire for age of onset of epistaxis, frequency and severity of epistaxis, subjective assessment of epistaxis therapy, precipitating factors, progression with age and patients´ habits with regard to care for their nasal mucous membranes. Severity of patients´ condition was graded by frequency and intensity of epistaxis and the need for repeat hospital admissions. Frequency and intensity of epistaxis was graded according the scale described by Bergler and coworkers [5]. The respective parameters were estimated prior to treatment, after treatment and on every follow-up visit. Assessment of therapy was aided by the use of a visual analog scale (VAS) with scales from 1- 6 (1 = excellent, 6 = poor). The results were analysed with the statistical software packages CSS:Statistica and SPSS 11.0.

RESULTS

The group consisted of 30 females and 19 males with an age range between 15 - 77 years (mean: 55 ± 16.2 years). Forty-seven of forty-nine patients showed three positive Curaçao-criteria, diagnosis of HHT may be regarded as certain in these patients. The remaining two patients fulfilled two positive Curaçao-criteria; diagnosis may therefore be regarded as likely. Arteriovenous malformations (AVM) in visceral organs were evident in 57% of the patients (pulmonary AVMs: 16 p.; hepatic AVMs: 10 p.; gastrointestinal tract: 9 p.; cerebral AVMs: 2 p.; ocular vascular lesions: 2 p.; urogenital tract: 1p.), who had undergone screening or were treated for visceral AVMs before. Nine individuals had refused screening despite being fully informed about the nature of HHT. All patients had recurrent epistaxis, source of nasal hemorrhages were telangiectases of the nasal mucosa, which could be found in all patients (Figure 1). Telangiectases of the skin and the mucous membranes were found in 96% of the cases, family history was definitely positive in 80% of the cases and likely in the rest. During the observation period 4/49 patients died; the cause of death was related to HHT in one case (liver failure because of multiple hepatic AVMs).

Age of Onset

In the entire group of patients onset of recurrent epistaxis varied from 4 - 64 years, with a mean age of 35 years (median: 33, standard deviation: 14.99), however first episodes of epistaxis had started in 22/49 patients (45%) in childhood. At the age of 50 years 88% of the patients had recurrent epistaxis. Four female patients had stated, that onset of epistaxis was triggered by pregnancy, one further female patient stated that epistaxis started after she had reached menopause. One female patient could delineate that epistaxis was set off by a continous medication with Aspirin® as anticoagulant prophylaxis after a myocardial infarction, the rest of the patients could not relate onset of epistaxis to a specific event. In 93% of the patients epistaxis was the first symptom of HHT. Initial presentation at a health care institution for treatment of epistaxis was 39 years on average (mean value: 39.21, median: 40, standard deviation: 15.1). The average age, at which the diagnosis of HHT was made for the first time was 42 years (mean: 42.4, median: 43, standard deviation: 13.7). However in some cases the delay between onset of recurrent epistaxis and the diagnosis of HHT accounted for more than 10 years.

Frequency and Intensity

Prior to treatment in our department 22% of the patients had monthly episodes of epistaxis, 46% of the patients had weekly episodes of epistaxis, 18% of the patients had daily episodes of epistaxis and 14% of the patients were unable to give any statements. Frequency of epistaxis was subject to changes and fifty-two percent of the patients had experienced daily episodes of epistaxis at least once in their lifetime. In half of the patients episodes of epistaxis lasted between 1-10 minutes, the other half had recorded a duration between 11-30 minutes, only one patient had experienced episodes of epistaxis, which lasted longer than half an hour. More than two thirds of the patients stated that intensity and frequency of epistaxis increased with advancing age. Only three patients had noted a reduction of epistaxis intensity and frequency with advancing age. Epistaxis could be triggered most commonly by emotional stress; other promoting factors are compiled in Table 1.

Table 1. Epistaxis-promoting factors in HHT. Most commonly epistaxis was provoked by emotional stress, but also bending over and physical activities easily caused epistaxis. Epistaxis affects all aspects of life in HHT patients and has a significant impact on the health-related quality of life perception.

Promoting Factor	**Percentage**
Emotional Stress	64%
Bending Down	45%
Physical Activity/Work Out	33%
Alcoholic Beverages	31%
Dry Climate/Changes in Climate	14%
Sneezing	10%
Beverages with a high Vitamin C content	7%
Cigarette Smoke	5 %

Epistaxis history

Prior to initial presentation in our department 26/49 patients (53%) had been treated in other institutions, where at least one interventional treatment had been performed. Most commonly these patients had been treated by laser therapy (14/26), however none of these patients had an improvement that lasted longer than 6 months. Laser systems, which had been used, were Argon lasers, CO_2 lasers and Diode lasers. Eight patients had received arterial embolization or ligation of the maxillary artery and their respective branches, thirteen patients had received septodermoplasty and two patients had received Fibrin injections into the septal mucosa. Eleven patients had received combinations of treatment. Only patients, who had been treated by septodermoplasty, had an improvement of epistaxis which lasted longer than 6 months; in four of these patients improvement lasted longer than 5 years. However septodermoplasty was not without side effects, three patients had developed a septal perforation, one patient had an oronasal fistula, one patient had nasal stenosis and in one patient the transplant had sloughed off.

Septal perforations

Including the above mentioned cases a total number of eleven patients had a perforation of the nasal septum as a result of multiple treatments for epistaxis. In six cases the perforation had been the result of multiple coagulations, in three patients perforations had occurred after septodermoplasty, one patient had developed a perforation after a submucosal injection of fibrin glue into the septal mucosa and one patient could not recall the cause of his perforation. When questioned whether the septal perforation had any influence on frequency and intensity of epistaxis, only four patients answered that the septal perforation had worsened epistaxis. Three patients complained about acoustic irritations through the septal perforation (the patients experienced a "whistling" noise on inspiration). Although the patients did not seem to be irritated much by their septal perforation, objective data showed that patients with septal perforations had more severe epistaxis than patients with an intact septum. Patients with an intact nasal septum usually had significant improvement of epistaxis after two Nd:YAG laser treatment sessions, whereas patients with a septal perforation needed an average of 4.6 laser sessions to achieve the same result.

Conservative therapy

Thirty-seven out of forty-nine patients used nasal ointments for lubrication of the nasal mucosa on a daily basis, on an average the patients spent 22.2 minutes a day with the care for their noses. Thirty-three of these thirty-seven patients (89%) stated that the continuous lubrication of the nasal mucosa reduced epistaxis. The following ointments were used: "Soft Nasal Ointment" (contents: menthol, lanolin and vaseline, 3-5 times daily), "Bremen Nose Ointment" (contents: chlorhexidinacatate, propylenglycole, miglyole 812 and lanolin 3-5 times daily), "Dexpanthenol Ointment" (bid), "Estriol Ointment" (contents: estriol, peanut oil, vaseline and lime oil, three times daily) and "Cod Liver Oil-Ointment" (tid). Side effects of some nose ointments were unpleasant odours (e.g., cod-liver oil ointment) and irregular uterine hemorrhages in women using estriol ointment. Nine women had been treated by systemic hormone therapy, 7/9 patients stated that it had no benefitial effect, 2/9 patients stated that systemic hormone therapy had a beneficial effect for up to 6 months. Forty-one percent of the patients suffered from iron-deficiency anaemia at initial presentation. Twenty-nine patients were on a regular medication with oral iron supplementation and twenty-one patients had received blood transfusions. As a result of multiple blood transfusions, two patients had suffered a hepatitis B infection and one patient had suffered a hepatitis C infection.

Nd:YAG laser therapy

In cases of mild-moderate epistaxis endoscopic Nd:YAG laser therapy was recommended, but also the majority of patients with moderate-severe epistaxis explicitly wished to be treated with the Nd:YAG laser. All procedures were performed under general anaesthesia according to recommendations of Eberhart and coworkers [6]. General anaesthesia and intubation allowed to shield the airway from blood aspiration and to treat larger amounts of telangiectases due to a better exposure. After endoscopy of the nose in a decongested state telangiectases were treated with Nd:YAG laser (power settings: 15 to 20 W for 0.1 to 0.5 seconds). Depending on the tissue reaction, the laser energy was gradually increased to 25 Watts. The laser light was delivered by a flexible bare fiber (diameter: 0.6mm). Wherever possible, feeding vessels (Figures 1 and 2) were coagulated prior to coagulation of the central telangiectases. Bilateral coagulations on the septum were deliberately avoided to prevent septal perforations. At the end of each operation the

Figure 1. View into the right nasal cavity of a 25-year-old HHT patient with a 30°-angled rod lens endoscope. Multiple telangiectases can be seen on the septal mucosa and the lateral nasal wall. Recurrent epistaxis originates from these telangiectases, either spontaneously or after minimal trauma.

Figure 2. Microscopic view of the left nasal septum (magnification: x 4.6). The 0.6 mm bare fiber is aimed at multiple telangiectases on the septal mucosa. The Nd:YAG laser light is delivered through the flexible fiber and is used to coagulate telangiectases in a centripetal way. A distance of 2-3 mm should be kept between the fiber and the telangiectases to avoid direct contact and accidental carbonisation. The blanched patches indicate mucosal areas which have already been treated with Nd:YAG laser light.

Figure 3. Endoscopic view of a dermal graft to the left nasal septum. The dermal graft is healed in well and shows stable conditions. The graft itself is free of telangiectasia, whereas a small patch of mucosa in the anterior portion, which had not been covered by the dermal graft, shows recurrence of telangiectasia. Recurrence of epistaxis in patients who have undergone septal dermoplasty is, among other reasons, promoted by neoformation of telangiectasia in previously untreated patches of mucosa.

nasal cavity was sealed with an ointment, nasal packing was generally avoided. Nd:YAG laser therapy reduced frequency and intensity of epistaxis in 38 patients (77.5%). For a period of time between 6-12 months a reduction of epistaxis frequency and intensity of 80–90%, compared to the initial state, could be achieved in 28/38 (57%) patients. Seven patients were judged to have a good treatment result (reduction > 50%) and three

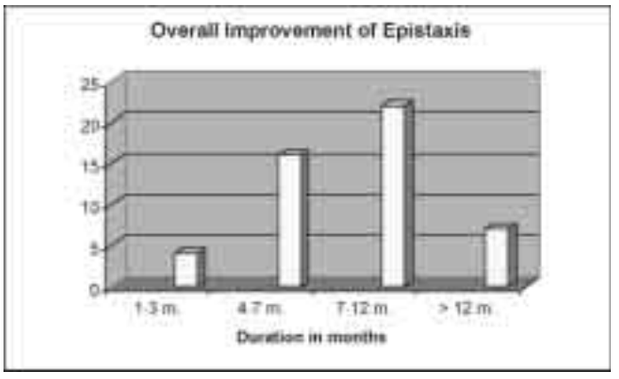

Figure 4. Overall treatment results in epistaxis therapy. Most patients could be improved by a combination of continous lubrication of the nasal mucosa with ointments in combination with Nd:YAG laser therapy. Characteristics of the group, who responded well to this type of therapy, were an intact nasal septum and mild-moderately severe epistaxis. Through conventional surgery or combined therapies alleviation of epistaxis could also be achieved in patients with moderate-severe epistaxis, who frequently had also septal perforations.

patients were found to have a moderate treatment result (reduction < 50%) An average of 2.7 endoscopic Nd:YAG laser sessions was necessary to achieve the above mentioned results (median: 2; standard deviation: 2,5). Three patients developed a septal perforation as a result of Nd:YAG laser therapy, two patients developed synechiae. In a subjective assessment the patients rated Nd:YAG laser therapy with an average mark of 1,8 (best mark: 1; worst mark: 6; median: 2; standard deviation: 0,9).

Conventional surgery and arterial embolization

Eleven patients with moderate to severe epistaxis could not be treated sufficiently with the Nd:YAG laser. Seven patients received septodermoplasty or modified septodermoplasty and 4 patients were treated by transfemoral, arterial embolization of the maxillary artery and her branches. Six patients needed combinations of these treatment modalities to reduce epistaxis to an amount, which allowed them to resume their normal daily life. Overall satisfactory reduction of epistaxis could be achieved in 89% of the patients (Figure 4). The duration of successful therapy lasted between 2 - 39 months.

DISCUSSION

Rendu [7], Osler [8] and Weber [9] described a disease, which is characterized by the triad of epistaxis, hereditary pattern and multiple mucocutaneous telangiectases. It was Hanes, who proposed the term hereditary, hemorrhagic telangiectasia, which is now most commonly used [10]. HHT has a worldwide distribution [11] and it affects all races [12]. The incidence of the disorder varies in a wide range [12, 13], data for Germany are not available so far.

Genetic alterations in HHT have been described for chromosomes, which influence the TGF-β pathway [14]. The genetic defects induce a dilatation of capillaries accompanied by incomplete smooth muscle coating of the vessels [15]. Predilection site for hemorrhages is the nasal mucosa [16] and the initial symptom of the disease is epistaxis in 90 % of all cases. Epistaxis has been described as an early marker for HHT [17], which is of importance with regard to the identification of potential HHT bearers. Identification of affected families renders the possibility to screen family members for visceral AVMs and to prevent AVM-associated morbidity [18]. Although visceral AVMs represent the greatest danger for HHT patients, with regard to massive hemorrhages, stroke, paradoxical embolism, liver or heart failure, it is epistaxis, which is the most troublesome symptom. Preliminary results of a health-related quality of life assessment in HHT patients clearly showed, that epistaxis had the greatest negative impact on their quality of life perception (our unpublished data).

In a first step of the presented analysis the natural history of epistaxis was evaluated and it did not show obvious differences to previously analysed groups from the United States of America or the Netherlands [15, 17]. Similarily to both of these investigations we had more female than male patients, the age of onset of recurrent epistaxis was between third and fifth decade of life and overall frequency and intensity of epistaxis were within the described ranges. In conclusion with AAssar and coworkers [17] we would like to state that epistaxis is a progressive symptom, based on the finding that the majority of our patients reported that frequency and intensity of epistaxis increased with advancing age. This statement however is contrary to the findings of Haitjema and coworkers [15], but may be explained by the fact, that Haitjema and coworkers [15] not only analyzed HHT patients, but also asymptomatic relatives. On the other hand we are in conclusion with Haitjema and coworkers [15] with regard to the observation that hormonal changes seem to have a rather deleterious than benefitial effect on epistaxis in HHT patients.

Therapy of epistaxis in HHT is controversial, or it should rather be said that no previously described therapy offers permanent relief. Anterior and posterior nasal packing, electrocautery, Saunders' plasty, arterial embolization, arterial ligation, cryotherapy, brachytherapy, cautery with infra-red light, topical and systemic application of estrogens, photodynamic therapy, laser therapy and in refractory cases the closure of the nares are just some examples of what has been tried. There is no causative cure for epistaxis in HHT, which stresses the necessity to develop reliable symptomatic therapies. In an earlier report our group [19] analysed all previously described treatment options and found that a generally accepted, uniform treatment concept did not exist. According to this analysis only septodermoplasty and laser therapy achieved a significant reduction of epistaxis frequency and intensity, lasting longer than 6 months. Part of the equation was an acceptable amount of unwanted effects. Septodermoplasty as well as Nd:YAG laser therapy bear the risk of septal perforations, but this risk is part of every interventional therapy, as could be shown in our patient, who had received the fibrin glue injection.

Many lasers have been used for the treatment of epistaxis in HHT, among which the Nd:YAG laser, the Argon laser and the KTP laser have shown good results, whereas the CO_2 laser was not found to be convincing [11, 20-23]. Nd:YAG laser light induces larger areas of fibrosis than other lasers [24], a fact that may explain our good experiences with this type of laser. In a retrospective study it is difficult to decide, which part of the treatment was most benefitial, because patients have to remember therapy sessions over a period of time of more than 5 years. However patients seemed to be quite content with the combination of regular nasal lubrication and endoscopic Nd:YAG laser therapy. The presented results of Nd:YAG laser therapy are slightly better than our previous evaluations [22] and may be explained by the fact, that HHT patients are now treated according to a uniform algorithm in our institution. Elements of this algorithm are the avoidance of nasal packing, the continous use of lubricants, the endoscopic assessment of endonasal telangiectatic disease prior to the operation, operations in general anesthesia, the use of the Nd:YAG laser for mild to moderate epistaxis, septodermoplasty for severe epistaxis and the limitation of arterial embolization of the maxillary artery and their branches to cases of intractable epistaxis. Closure of the nares or forehead flaps have so far neither been necessary in the management of our HHT patients nor would the patients have accepted these procedures, because of the fear of permanent nasal obstruction.

A cheap, but equally invaluable element of epistaxis therapy in HHT patients to our point of view is nasal lubrication with ointments. Lubricants effect that nasal vessels are shielded from trauma and exsiccation. This allows a better exposure during the endoscopic laser sessions and, because of the reduction of intraoperative bleeding, a higher number of vessels can be treated. At conclusion of a laser session, the nasal cavity can be sealed with ointments instead of packing the nose with gauze [25]. Postoperatively and in the follow-up lubrication should be continued, which was well accepted by our patients, although it was time consuming. Our patients spent an average of 22 minutes per day with the care of their nasal mucous membranes and 89% of those, who did that, stated that it reduced epistaxis. McCaffrey and coworkers [26] stated that lubricants had little effect on epistaxis in HHT as sole treatment. In combination with interventional therapies or supplemented with estriol, however, lubricants may bring greater benefit than other types of conservative treatment [25, 27]. With the exception to lubricants, iron and folate supplementation or transfusions little evidence could be found among the analysed group, that other types of conservative treatment

were helpful in reducing epistaxis. Topical or systemic estrogen therapy was judged as ineffective in the majority of our patients, who had been treated with hormones, and those two patients, who had registred a positive effect, stated that this effect lasted only 6 months. The findings are in conclusion with the findings of the only double-blind study, which has been performed with hormones in HHT patients so far [28]. Prescription of topical or systemic hormone therapy in HHT can therefore not generally be recommended or rejected; it should rather be decided on an individual basis.

In the presented group epistaxis could be alleviated for a period of time, which ranged between 2 and 39 months, with the majority of the patients noticing an improvement for 7-12 months. Six patients had an improvement, which lasted longer than 12 months. These results show that it is extremely difficult to achieve a longer lasting reduction of HHT-related epistaxis, but the overall improvement corresponds to the results, which have been achieved with other endoscopically applicable methods [29]. The most recent developments in HHT-related epistaxis therapy are the use of silastic obturators for temporary closure of the nares, destruction of telangiectases with the Ultracision, -Harmonic Scalpel, external beam radiation, intranasal application of tranexamic acid and coagulation of telangiectases with the Argon-Plasma Coagulator in combination with the topical application of estriol ointment [27, 30-33]. With a few exceptions most of theses reports are case reports or case series with a limited follow-up, the value of these new methods cannot be judged at this moment. Currently, after more than forty years of experience with septal dermoplasty and after twenty years of experience with laser therapy for the treatment of epistaxis in HHT it can be said that only these two methods have so far stood the test of time. ENT-surgeons however should keep on developing new treatment strategies, which would definitely be appreciated by patients and medical professionals.

CONCLUSION

Natural history of HHT-related epistaxis in German patients is similar to those of HHT patients in other countries. Epistaxis often begins in childhood, becomes recurrent in the fourth decade of life and seems to progress with advancing age. Endoscopic Nd:YAG laser therapy and the use of lubricants can significantly reduce frequency and intensity of epistaxis for periods of 6–12 months in cases of mild–moderate epistaxis. More severe forms of epistaxis in HHT will require combinations of therapies including blood transfusions, laser therapy, septal dermoplasty and arterial embolization.

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