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# Epistaxis in hereditary haemorrhagic telangiectasia*

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SUMMARY

*Hereditary haemorrhagic telangiectasia (HHT) is characterized by easily bleeding telangiectases of the skin and mucosa. Epistaxis is the most common symptom of HHT. Larger arteriovenous malformations (AVM) occur in the lungs (in up to 33% of the patients), brain (in up to 11% of patients), and liver. These may cause severe complications which can be prevented by early therapy. To gain insight in the characteristics of epistaxis in HHT, 171 persons were investigated, who either had HHT or participated in a screening programme for relatives of HHT patients. Of these, 58 persons had HHT. Epistaxis without signs of HHT was present in 12 persons, whereas 10% of HHT patients did not have epistaxis. Seventeen HHT patients with epistaxis had visited an otorhinolaryngologist before, without a correct diagnosis of HHT being made. Telangiectases were most common on lips, tongue, the nasal septum, and the turbinates. In view of the prevalence of visceral AVM and the associated complications, HHT patients presenting to an otorhinolaryngologist should be encouraged to engage in a screening programme for these AVM.*

*Key words: hereditary haemorrhagic telangiectasia, Rendu-Osler-Weber syndrome, epistaxis, telangiectasis*

## INTRODUCTION

Hereditary haemorrhagic telangiectasia (HHT) is an autosomal dominant disease, characterized by easily bleeding telangiectases of the skin and mucosa. Recently, a mutation in the gene encoding for TGF-ß has been shown in some but not in all HHT patients (McAllister et al., 1994). Other genetic subtypes with different clinical manifestations probably exist (Heutink et al., 1994). Larger arteriovenous malformations (AVM) also occur in parenchymatous organs, especially lungs (PAVM), brain (CAVM) and liver. Their prevalence might be higher than previously estimated. In a recent study in relatives of HHT patients we found PAVM in 33%, and CAVM in 11% (Haitjema et al., 1995). These AVM may cause serious complications; bleeding from PAVM is rare but potentially life-threatening. Additionally, PAVM are associated with paradoxical emboli, with an estimated annual risk for stroke of 1.5% (White et al., 1988), and infected metastatic abscesses (Burke et al., 1986). Cerebral abscesses occur in 5% of patients with PAVM (Adams et al., 1977). In patients with CAVM but without HHT, the annual risk of cerebral bleeding is 2–3%. Whether this risk is higher in HHT patients is unknown. These complications can mostly be prevented by early treatment (White et al., 1988). Therefore, early diagnosis is warranted. Epistaxis is the most common feature of HHT, and often difficult to control. Anterior nasal packing, electrocoagulation, dermoplasty, hormonal treatment, arterial clipping, embolisation, and laser coagulation all have proved to have only temporary effects (McCaffrey et al., 1977; Reilly and Nostrant, 1984; Parnes et al., 1987). The problems encountered in the management of epistaxis in these patients are illustrated by the fact that even brachytherapy (Pohar et al., 1993) and closure of the nostrils (Young's procedure; cf., Hosni and Innes, 1994) have been used. To investigate the prevalence of mucosal telangiectases and epistaxis in HHT, as well as the characteristics of epistaxis, we studied HHT patients as well as their relatives undergoing screening for presence of the disease.

## PATIENTS AND METHODS

All persons who visited our clinic with HHT or as part of a screening programme for relatives of HHT patients, were investigated by one otorhinolaryngologist (FD). Relatives of HHT patients visiting our clinic are actively encouraged to take part in

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a screening programme aimed at early diagnosis of HHT and associated PAVM and CAVM. A total of 171 persons were investigated, 101 females and 70 males, with a mean age of 29.3 years (range: 1–77 years).

The oral mucosa was inspected for telangiectases. Nasal endoscopy was performed for inspection of the nasal mucosa. All persons were screened for HHT or associated arteriovenous malformations as published previously (Haitjema et al., 1995). In December 1994, all persons were contacted by telephone to obtain information on their epistaxis. A standard questionnaire was used.

HHT was diagnosed when characteristic telangiectases were present, or when visceral AVM were found in persons with a family history of HHT. Epistaxis, however, was not required for the diagnosis.

## RESULTS

Of the 171 persons investigated, 75 had neither HHT nor epistaxis, and in 13 the data available were insufficient for analysis. Of the 83 persons remaining, 58 had HHT, 12 did not have HHT, and in 13 no certain diagnosis could be made (Table 1). This was due to doubtful or atypical cutaneous telangiectases in seven persons, doubtful or atypical mucosal telangiectases in four persons, possibly a small PAVM in one person, and possibly gastrointestinal telangiectases in one person.

Table 1. Presence of HHT and epistaxis in all patients with complete data available.

| | epistaxis | no epistaxis |
|---|---|---|
| HHT present | 52 | 6 |
| HHT absent | 12 | 75 |
| HHT unknown | 4 | 9 |

Four out of six patients with HHT but without epistaxis, had telangiectases in the nasal mucosa, and two only in the oropharyngeal mucosa. In two out of 12 persons with epistaxis but without HHT, a venectasia at the *locus Kieselbachii* was seen. Nineteen out of 52 patients with HHT and epistaxis had visited an otorhinolaryngologist before, but in only two patients the correct diagnosis of HHT was made.

The age of onset in HHT patients with epistaxis is shown in Figure 1. The frequency of epistaxis is shown in Table 2.

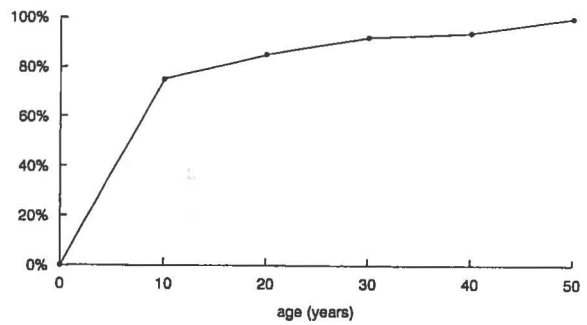


Figure 1. Age of onset of epistaxis in HHT patients with epistaxis (n=52).

Table 2. Frequency of epistaxis in all persons with epistaxis and HHT patients with epistaxis.

| incidence of epistaxis (per month) | all persons with epistaxis (n=68) | HHT patients with epistaxis (n=52) |
|---|---|---|
| <1 | 10 | 6 |
| 1–10 | 34 | 26 |
| 11–20 | 10 | 7 |
| 21–30 | 11 | 10 |
| >30 | 3 | 3 |

Table 3. Factors influencing frequency and seriousness of epistaxis in HHT patients with epistaxis (30 females and 22 males). Only reported beneficial or deleterious effects are shown.

| | deleterious effect (No. of patients) | beneficial effect (No. of patients) |
|---|---|---|
| puberty | 6 | 2 |
| menstruation | 9 | - |
| oral anticonceptives | - | 2 |
| pregnancy | 9 | - |
| menopause | 5 | - |
| psychological stress | 5 | - |
| alcohol | 6 | - |
| temperature changes | 5 | - |

Table 4. Localisation of telangiectases in patients with HHT (n=58).

| | no telangiectases | telangiectases present | | | |
|---|---|---|---|---|---|
| | | few (<5) | moderate (5-25) | many (>25) | total (%) |
| lips | 25 | 14 | 16 | 3 | 33 (57%) |
| tongue | 21 | 15 | 17 | 5 | 37 (64%) |
| gingiva | 44 | 11 | 3 | - | 14 (24%) |
| buccal mucosa | 41 | 12 | 4 | 1 | 17 (19%) |
| palate | 46 | 6 | 5 | 1 | 12 (21%) |
| pharynx | 52 | 4 | 2 | - | 6 (10%) |
| vestibulum nasi | 31 | 11 | 11 | 5 | 27 (47%) |
| nasal septum | 11 | 16 | 26 | 5 | 47 (81%) |
| middle turbinate | 32 | 10 | 13 | 3 | 26 (45%) |
| inferior turbinate | 17 | 14 | 21 | 6 | 41 (71%) |
| posterior nasal mucosa | 52 | 4 | 2 | - | 6 (10%) |

Thirteen patients have experienced unilateral bleeding, the remainder have had bilateral nasal bleeding. Factors influencing epistaxis are shown in Table 3.

Epistaxis was progressive in 19 patients. The blood loss was classified as slight by 29 persons, as moderate by 20 persons, and as severe by three persons. Iron suppletion was used by 10 patients, three of these had required regular blood transfusions. Localisation of telangiectases in the 58 patients with HHT is shown in Table 4.

## DISCUSSION

In this study, recurrent epistaxis has been observed in 90% (52/58) of HHT patients. This is in line with previous reports (Reilly and Nostrant, 1984; Peery, 1987; Assar et al., 1991). Of the patients eventually developing epistaxis, 85% have experien-

ced the first episode before the age of 21 years. It is important to realize that not every relative of a HHT patient with epistaxis has HHT, as illustrated by the 12 patients in our population with epistaxis but without HHT. Moreover, six patients without epistaxis did have HHT. Therefore, using the presence of epistaxis to decide which relatives of a HHT patient should be screened for PAVM and CAVM, as suggested previously by Assar et al. (1991), would be inaccurate.

Epistaxis was progressive in 19 patients. However, for all HHT patients with epistaxis no relationship existed between age and degree of epistaxis, nor was there any difference in degree of epistaxis between patients with PAVM or CAVM and those without. Thus, we cannot confirm previous reports on epistaxis being a progressive symptom of HHT (Assar et al., 1991). Others also find progression of epistaxis in a limited subgroup of HHT patients (McCaffrey et al., 1977; Peery, 1987).

An interesting but worrying observation is the fact that 17 patients visited an otorhinolaryngologist before, without the diagnosis of HHT being made. In view of the potentially serious complications of HHT discussed above, early recognition is important in order to be able to find and treat associated PAVM and CAVM. When confronted with HHT patients, otorhinolaryngologists should inquire whether they have been screened for PAVM and CAVM, and whether their relatives have been investigated.

When screening relatives of HHT patients for presence of the disease, telangiectases will most frequently be found on the lips, tongue, nasal septum, and turbinates (cf., Table 4). Therapy of epistaxis in HHT patients is known to be troublesome, but there are some new developments. Hormonal treatment of epistaxis is interesting: Koch et al. (1952) reported on the beneficial effect of oestrogens upon epistaxis in HHT patients. Harrison (1964) postulated that a thick layer of squamous epithelium overlying nasal telangiectases develops during oestrogen therapy. However, the only double-blind trial concerning this treatment did not show any effect of oestrogen on epistaxis (Vase, 1981). Recently, the combination of oestrogens and progestagen was shown to be effective in controlling blood loss in HHT patients with gastrointestinal telangiectases (Cutsem et al., 1993). It is therefore tempting to extend this treatment to patients with severe epistaxis, although its efficacy has up to now not been the subject of study. Another more recent development is the use of cyclocaproic acid (Saba et al., 1994), although its effectiveness has been questioned (Korzenik et al., 1994). It is, however, a well-tolerated non-invasive treatment, and we feel a trial might be indicated in severe epistaxis, although data on the safety of long-term use of cyclocaproic acid are not available (Phollips, 1994).

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REFERENCES

1. Adams HP, Subbiah B, Bosch EP (1977) Neurologic aspects of hereditary haemorrhagic telangiectasia (report of two cases). Arch Neurol 34: 101–104.
2. Assar OS, Friedman CM, White RI (1991) The natural history of epistaxis in hereditary haemorrhagic telangiectasia. Laryngoscope 101: 977–980.
3. Burke CM, Safai C, Nelson DP, Raffin TA (1986) Pulmonary arteriovenous malformations: A critical update. Am Rev Respir Dis 134: 334–339.
4. Cutsem E, Rutgeerts P, Vantrappen G (1993) Long-term effect of hormonal therapy for bleeding gastrointestinal vascular malformations. Eur J Gastroenterol 5: 439–443.
5. Haitjema T, Disch FJM, Overtoom TTC, Westermann CJJ, Lammers JWJ (1995) Screening family members of patients with hereditary haemorrhagic telangiectasia. Am J Med 99: 519–524.
6. Harrison DFN (1964) Familial haemorrhagic telangiectasia: 20 cases treated with oestrogen. Quart J Med 33: 25–38.
7. Heutink P, Haitjema T, Breedveld GJ, Janssen B, Sandkuijl LA, Bontekoe CJM, Westermann CJJ, Oostra BA (1994) Linkage of hereditary haemorrhagic telangiectasia to chromosome 9q34 and evidence for locus heterogeneity. J Med Genetics 31: 933–936.
8. Hosni AA, Innes AJ (1994) Hereditary haemorrhagic telangiectasia: Young's procedure in the management of epistaxis. J Laryngol Otol 108: 754–757.
9. Koch HJ, Escher GC, Lewis JS (1952) Hormonal management of hereditary haemorrhagic telangiectasia. JAMA 149: 1376–1380.
10. Korzenik JR, Topazian MD, White RI (1994) Treatment of bleeding in hereditary haemorrhagic telangiectasia with aminocaproic acid. N Engl J Med 331: 1326.
11. McAllister KA, Grogg KM, Johnson DW, et al. (1994) Endoglin, a TGF-B binding protein of endothelial cells, is the gene for hereditary haemorrhagic telangiectasia type 1. Nature Genetics 8: 345–351.
12. McCaffrey TV, Kern EB, Lake CF (1977) Management of epistaxis in hereditary haemorrhagic telangiectasia. Review of 80 cases. Arch Otolaryngol 103: 627–630.
13. Parnes LS, Heeneman H, Vinuela F (1987) Percutaneous embolization for control of nasal blood circulation. Laryngoscope 97: 1312–1315.
14. Peery WH (1987) Clinical spectrum of hereditary haemorrhagic telangiectasia (Osler-Weber-Rendu disease). Am J Med 82: 989-997.
15. Phollips MD (1994) Stopping bleeding in hereditary telangiectasia. N Engl J Med 330: 1822–1823.
16. Pohar S, Mazeron JJ, Ghilezan M, Le Bourgeois JP, Pierquin B (1993) Management of epistaxis in Rendu-Osler disease: Is brachytherapy effective? Int J Radiation Oncology Biol Phys 27: 1073–1077.
17. Reilly PJ, Nostrant TT (1984) Clinical manifestations of hereditary haemorrhagic telangiectasia. Am J Gastroenterol 79: 363–367.
18. Saba HI, Morelli GA, Logrono LA (1994) Treatment of bleeding in hereditary haemorrhagic telangiectasia with aminocaproic acid. N Engl J Med 330: 1789–1790.
19. Vase P (1981) Estrogen treatment of hereditary haemorrhagic telangiectasia. Acta Med Scand 209: 393–396.
20. White RI, Lynch-Nyhan A, Terry P, Buescher PC, Farmlett EJ, Charnas L, Shuman K, Kim W, Kinnison M, Mitchel SE (1988) Pulmonary arteriovenous malformations: Techniques and long-term outcome of embolotherapy. Radiology 169: 663–669.

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