Report

Skin and mucosal telangiectatic lesions in hereditary hemorrhagic telangiectasia patients

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Introduction

Hereditary hemorrhagic telangiectasia (HHT), also known as Osler-Weber-Rendu disease, is an inherited autosomal dominant condition characterized by vascular malformations. The malformations are caused by dysfunctional vessel growth and repair and appear as telangiectatic lesions in the skin and mucosa and as arteriovenous malformations (AVMs) in the visceral organs.¹

Four different genes have so far been identified with pathogenic variants responsible for HHT. Mutations in ENG (OMIM 131195, HHT1) and ACVR1 (OMIM 601284, HHT2) are seen in patients with HHT1 and HHT2, respectively.²³ Mutations in SMAD4 are seen in patients with a rare combination of HHT and juvenile polyposis syndrome (OMIM 600993, JP-HHT).⁴ Most recently, a mutation in GDF2 is related to an HHT-like syndrome that shows some overlap with classical HHT but has a distinct clinical manifestation.⁵

Recurring epistaxis is present in 95% of patients with HHT, while the prevalence of telangiectatic lesions in the skin and mucosa increases with age.⁶ Visceral AVMs are mainly pulmonary (PAVM), hepatic (HAVM), and cerebral (CAVM) and are important to recognize as they can cause serious complications (especially PAVM) that could be prevented with proper treatment. It is known that the manifestations of PAVM, CAVM, and HAVM vary with the subtypes of HHT such that patients with HHT1 have a higher prevalence of PAVM and CAVM, while patients with HHT2 have a higher prevalence of HAVM.⁷,⁸

Telangiectatic lesions are present in 75% of patients with HHT,⁹ and although the anatomic locations of the lesions have been described in some studies,⁶,¹⁰–¹² little is known about the distribution and formation of telangiectatic lesions in patients with HHT. The diagnostic criteria for HHT (Curacao Criteria¹³) include the presence of multiple telangiectatic lesions, recurrent spontaneous epistaxis, visceral AVMs, and first-degree relative with HHT. If at least three of these four criteria are met, the patient is considered to have definite HHT; if two criteria are met, the HHT diagnosis is possible. Although the Curacao
Criteria were defined in 2000, it is still not defined what qualifies as “multiple” telangiectatic lesions. Furthermore, the diagnostic criteria only describe the common sites for telangiectatic lesions (lips, oral cavity, fingers, and nose) and not the appearance of the lesions themselves. Telangiectatic lesions can occur in other anatomical sites as well, and a better understanding of their appearance in HHT is an important component of the diagnostic workup.

**Objective**

The aims of the study were:

- To describe the characteristics of telangiectatic lesions in patients with HHT.
- To investigate whether the lesions were bothersome to the patients.
- To describe the distribution and total number of telangiectatic lesions and their relation to HHT subtype (HHT1/HHT2) and patient gender.

**Materials and Methods**

The study included 34 adult patients with a verified HHT diagnosis who were examined at the HHT Center at Odense University Hospital, Denmark. The patients underwent a standard examination to detect skin telangiectatic lesions on the body surface and a standard ENT examination to detect telangiectatic lesions in the head and neck area including facial skin, skin of the ears, lips, eyelids, nasal cavity, and oral cavity. The nasal cavity was examined using a rigid endoscope (Hopkins). Pictures of the telangiectatic lesions in the skin were documented using a Canon Powershot SS IS Digital Camera and in the nasal cavity using an Olympus Evis Exera III, CLV-190.

The number and sites of the cutaneous and mucosal telangiectatic lesions were calculated and noted by the same examiner, who was blinded to the patient’s subtype of HHT. In collaboration with the Department of Dermatology at Odense University Hospital, the telangiectatic lesions were described in a standardized manner as:

- Either capillary (small, pink, or reddish lesion) or venous (large, dark, or blue lesions).
- Either papular or macular (by palpation).
- Either linear or round. Linear lesions were categorized as “Single,” “Aborized,” or “Dilated.” Round lesions were categorized as “Single spot,” “Confluent,” “Radiating,” “Lacunar,” “Single/multiple tortuous,” or “Hemangioma-like.”
- Linear lesions described as “Besenreiser” and round cherry angiomas were not categorized as HHT lesions.

Table 1 provides a detailed description and pictures of the different lesions.

Patients were also asked to complete a questionnaire about any symptoms they experienced from their telangiectatic lesions and whether they had any cosmetic or other concerns.

The study was conducted from September to December 2019. The study was registered with, and approved by, the local ethics committee (S-20190059). Participation did not entail a change of treatment strategy. Patients gave informed consent to allow us to count and photograph their telangiectatic lesions and to use their questionnaire data.

Data are presented as numbers and percentages or means (age). Characteristics of HHT subtypes were compared using chi-squared test for categorical variables and t-test for continuous variables.

**Results**

Of the 34 patients included in the study, 18 patients had HHT1 and 15 patients had HHT2. An additional patient fulfilled the Curçaço criteria, but the HHT subtype was not clarified. Patient characteristics and symptoms are shown in Table 2. The mean age for HHT1 patients was 59.6 years (range 30–76 years) and for HHT2 patients was 56.9 years (range 28–78 years), with no significant difference between the two groups (Figure 1). Of the 34 included patients, 16 were men and 18 were women, and they were evenly distributed across HHT1 and HHT2. Mean age was similar for men (63.4 years) and women (57.4 years) \( (p = 0.5) \).

Reflecting the increasing symptoms from telangiectatic lesions over time, the patients had undergone various treatments before inclusion in the study; these were mainly applied to the nasal mucosa. Treatments included laser therapy, electrocauterization, regular Avastin treatment, Silastic nasal implants, and Young’s procedure (surgical closure of the nose).

Bleeding from the nasal cavity was experienced by 94.1% of the patients, and 47.1% of patients had been bothered by bleeding from the gums. Regarding cutaneous lesions, cosmetic concerns were the dominant problem described by 19 patients (55.9%). Bleeding occurred from lesions especially located at the lips in seven patients (20.6%), but patients also experienced bleeding from lesions on the skin of ears, cheeks, fingers, and feet. Two patients experienced local irritation and pain, and a further four patients reported soreness.

Table 3 shows the types and frequencies of telangiectatic lesions at various cutaneous and mucosal locations according to HHT subtype and gender. Most lesions were round, flat, or slightly elevated. All the patients examined had telangiectatic lesions on the cheeks, and lesions were also frequent on the forehead, external nose, outer ears, hands, and thorax. Telangiectatic lesions were found in the nasal cavity in 30 patients, but the total number of lesions here was not calculated as it was impossible to determine an exact number. Examination of the nasal cavity was not performed in three patients with bilateral Young’s procedure, and for one patient the documentation was not available.
Among the 18 HHT1 patients, 16 patients had lesions on their tongue (with a total of 222 lesions), and 14 patients had lesions in the oral mucosa (with a total of 314 lesions). Fewer of the 15 patients with HHT2 had lesions on the tongue (nine patients with a total of 38 lesions) and oral mucosa (eight patients with a total of 93 lesions). There was a significant difference between HHT1 and HHT2 patients in the number of mucosal lesions ($p = 0.034$).

The total number of counted cutaneous and mucosal telangiectatic lesions in the 18 HHT1 patients was 2655, compared to

**TABLE 1** Description and photographs of different types of telangiectatic lesions

| Round telangiectases | Simple round telangiectases |
|-----------------------|-----------------------------|
|                       | The simplest round telangiectasia is the “single spot” lesion, which represents a single entity only. Most are flat |

Tongue

Finger

Lower lip of a young patient
| Type            | Description                                                                                                                                 |
|-----------------|---------------------------------------------------------------------------------------------------------------------------------------------|
| Confluent round | A cluster of irregular single spot lesions that are surrounded by erythematous skin, making it difficult to distinguish the lesions from one another. Large lesions are elevated, but most cases are flat |
| Radiating round | Single spot lesions that feed off single or multiple blood vessels. “Star-shaped” and spider nevi are radiating telangiectases. The lesions are often slightly elevated |
| Lacunar round   | These are typically venous telangiectases due to their blue color. They are typically elevated, more circular, and large (generally >2 mm), with a negative glass tumbler test |
| Lesion Type          | Description                                                                 |
|---------------------|-----------------------------------------------------------------------------|
| Tortuous round      | Lesions appear round when viewed by the eye, but with magnification, the single spot appears to consist of several linear and dilated vessels that are coiled up, almost a glomerular-like structure. |
| Hemangioma-like round | Macroscopically resembling large, red, wart-like structures that have several small vessel openings that feed into the lesion. |
| Cherry angioma      | Round, highly red, and cannot be emptied. Not associated with HHT.          |
**TABLE 1 Continued**

| Linear telangiectases                  |
|----------------------------------------|
| **Dilated**                           |
| A linear vessel that seems more dilated and is often elevated |

| **Arborized**                          |
| A larger linear vessel that feeds off several visible smaller vessels |

| **Besenreiser**                        |
| Clearly dilated, elevated, and arborized venous vessels caused by venous insufficiency. Found on the lower extremities. Not associated with HHT |

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*External nose*  
*Right ear*  
*Right ankle*
TABLE 2 Characteristics of patients with hereditary hemorrhagic telangiectasia type 1 (HHT1) or type 2 (HHT2)

|                         | Total n = 34 | HHT1 n = 18 | HHT2 n = 15 | p value |
|-------------------------|--------------|-------------|-------------|---------|
| Male (%)                | 16 (47.0)    | 8           | 8           | 0.61    |
| Female (%)              | 18 (53.0)    | 10          | 7           |         |
| Mean age                | 58.6 years   | 59.6 years  | 56.9 years  | 0.63    |
| Anemia (%)              | 17 (50.0)    | 8           | 9           | 0.37    |
| PAVM (%)                | 9 (26.5)     | 8           | 1           | 0.015   |
| HAVM (%)                | 4 (11.8)     | 0           | 4           | 0.0087  |
| CAVM (%)                | 0 (0)        | 0           | 0           |         |
| GI-AVM (%)              | 6 (17.6)     | 2           | 4           | 0.25    |
| Previous treatment (%)  |              |             |             |         |
| Laser therapy           | 20 (58.8)    | 11          | 9           | 0.95    |
| Cauterization           | 21 (61.8)    | 11          | 9           | 0.95    |
| Avastin                 | 5 (14.7)     | 2           | 2           | 0.85    |
| Young’s procedure       | 4 (11.8)     | 1           | 3           | 0.21    |
| Other procedures        | 1 (2.9)      | 1           | 0           | 0.35    |
| Symptoms (%)            |              |             |             |         |
| Bleeding                |              |             |             |         |
| Nasal cavity            | 32 (94.1)    | 18          | 13          | 0.11    |
| Outer nose              | 1 (2.9)      | 1           | 0           | 0.35    |
| Gums                    | 16 (47.1)    | 9           | 5           | 0.33    |
| Lips                    | 7 (20.6)     | 5           | 2           | 0.31    |
| Tongue                  | 5 (14.7)     | 2           | 3           | 0.48    |
| Palate                  | 5 (14.7)     | 2           | 3           | 0.48    |
| Cheek                   | 4 (11.8)     | 2           | 2           | 0.85    |
| Ears                    | 2 (5.9)      | 1           | 1           | 0.89    |
| Hands                   | 3 (8.8)      | 2           | 1           | 0.66    |
| Gastrointestinal        | 4 (11.8)     | 1           | 3           | 0.21    |
| Feet                    | 1 (2.9)      | 1           | 0           | 0.35    |
| Pain                    | 2 (5.9)      | 1           | 0           | 0.35    |
| Tenderness              | 4 (11.8)     | 3           | 1           | 0.38    |
| Pruritus                | 4 (11.8)     | 4           | 0           | 0.051   |
| Cosmetic concerns       | 19 (55.9)    | 7           | 12          | 0.017   |

Abbreviations: AVMs, arteriovenous malformations; CAVM, cerebral; GI-AVM, gastrointestinal; HAVM, hepatic; PAVM, pulmonary.

Discussion

Telangiectatic lesions are defined as visible, dilated blood vessels in the skin and mucosa. They can occur as a natural part of aging but may also be associated with disease, for example, liver conditions, scleroderma, rosacea, and HIV infection.16 The morphology of telangiectatic lesions can be macular (flat) in appearance or more papular (elevated). They can be linear, but
TABLE 3 Anatomical location of telangiectatic lesions in patients with hereditary hemorrhagic telangiectasia type 1 (HHT1) or type 2 (HHT2) and by gender

| Location        | HHT1 N – 18 T/N (mean) | HHT2 N – 15 T/N (mean) | Men N – 16 T/N (mean) | Women N – 18 T/N (mean) |
|-----------------|------------------------|------------------------|-----------------------|-------------------------|
| Skin            |                        |                        |                       |                         |
| Forehead        | 9/150(17)              | 10/39(3.9)             | 10/166(17)            | 10/25(2.5)              |
| Cheeks          | 18/213(12)             | 15/284(19)             | 16/209(13)            | 18/300(17)              |
| Chin            | 10/47(4.7)             | 7/32(4.6)              | 7/21(3)               | 11/59(5.4)              |
| Eyelids         | 3/4(1.3)               | 4/5(1.3)               | 3/5(1.7)              | 5/6(1.2)                |
| Ears            | 16/651(41)             | 13/358(28)             | 14/589(42)            | 16/462(29)              |
| Lips            | 17/172(10)             | 13/117(9)              | 14/122(8.7)           | 17/183(11)              |
| Nose            | 15/458(31)             | 14/106(8)              | 16/187(12)            | 14/92(6.6)              |
| Thorax          | 12/83(6.9)             | 13/251(19)             | 11/135(12)            | 15/229(15)              |
| Feet            | 7/135(19)              | 4/117(29)              | 6/60(10)              | 5/192(38)               |
| Hands           | 16/699(44)             | 13/251(19)             | 13/656(50)            | 17/420(25)              |
| Mucosa          |                        |                        |                       |                         |
| Nasal cavity    | 16                     | 13                     | 13                    | 17                      |
| Oral cavity     |                        |                        |                       |                         |
| Tongue          | 16/222(14)             | 9/36(4.2)              | 12/48(3.8)            | 14/215(15)              |
| Oral mucosa     | 14/314(22)             | 8/93(12)               | 11/42(3.8)            | 11/105(9.5)             |
| Superior conjunctiva | 10/22(2,2)         | 9/18(2)                | 9/24(2,7)             | 11/19(1.7)              |

Note. N = number of patients with lesion; T = total number of lesions; mean T/N = the mean number of lesions presented in the site.

a round shape is much more common. Vessel dilatation increases with age, leading to the more popular appearance of the lesion. Diagnosis of HHT can sometimes be difficult, especially if the clinician is unfamiliar with the typical appearance of telangiectatic lesions in HHT. We found that especially the cutaneous telangiectatic lesions in HHT patients were mainly round and macular. In line with Folz et al.,11 who investigated the morphology and distribution of telangiectatic lesions in the nasal cavity, we found a large variety of lesion morphologies, with variations in both size and appearance.

Our study group comprised patients with HHT who required treatment due to severe bleeding, and thus our results do not necessarily reflect the true natural history of telangiectatic lesions. This is especially for lesions in the nasal mucosa, where treatment was common. This may have caused fewer visible lesions than in patients without previous treatment.

Few studies have investigated the distribution of telangiectatic lesions in HHT patients. We found that 100% of HHT1 and HHT2 patients had lesions on the cheeks while 89% of HHT1 patients and 87% of HHT2 patients had lesions on their hands. These results are in line with another study from Folz et al.10 that investigated the distribution of telangiectatic lesions in 70 patients with HHT. A limitation of our study is that we only investigated 34 HHT patients and only patients with HHT1 and HHT2. Folz included 70 HHT patients and all four types of HHT (HHT1, HHT2, JP-HHT, and HHT5), making their study more representative of HHT in general.

We found that men tended to have more lesions on the forehead, nose, and hands compared to women. This could be due to men more often having jobs that are physically demanding or with greater exposure to sunlight. A German study16 found that mechanical trauma and light-induced trauma (UV-light) were associated with the development of more lesions. They found that HHT patients with a higher degree of manual work had more lesions on their dominant hand and that HHT patients with greater exposure to sunlight had more lesions in sun-exposed areas (forehead and lips).

In line with our results, Letteboer et al.6 also reported an increasing number of lesions with patient age. HHT patients are thought to develop telangiectatic lesions due to "second-hits,"17,18 and this is believed to be one of the explanations for the increasing number of lesions with age.

It is well known that telangiectatic lesions in the mucosa can cause bleeding especially epistaxis. However, bleeding can also occur from other mucosal lesions in the skin, for example, the lips, skin of face/fingers, and gums. Skin lesions may also lead to other concerns, but this is less well described. In the current study, we found that more than 50% of the patients had cosmetic concerns. Furthermore, the skin lesions caused local symptoms such as pain and pruritus.

Conclusion

This study provides a snapshot of the distribution of telangiectatic lesions in men and women with HHT1 or HHT2. The classic appearance of a telangiectatic lesion was a round, macular spot of 1–2 mm, but other appearances were common, such as radicular, tortuous, or simply dilated capillaries. When patients present with this type of lesion, the HHT diagnosis should be considered. The presentation of lesions may vary a little between HHT1 and HHT2 patients but not in such a way that allows the morphology and location of the lesions to predict the HHT subtype. As expected, the number of telangiectatic lesions increased with age in patients with HHT1 and HHT2.

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