Capillaroscopy of the dorsal skin of the hands in hereditary hemorrhagic telangiectasia

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Summary

Background: Cutaneous telangiectases are manifestations of hereditary hemorrhagic telangiectasia (HHT), a dominantly inherited disorder. Telangiectases have been studied by skin biopsy, and recently by nailfold capillaroscopy.

Aim: To confirm the diagnostic role of nailfold capillaroscopy, and assess the value of skin capillaroscopy of the dorsum of the hands in HHT.

Design: Prospective clinical investigation.

Methods: Using a Wild Heerbrugg-M650 microscope, we studied the nailfolds and dorsum of the hands of 88 patients (37 females, 51 males, mean age 39.7 ± 18.4 years), including 85 with positive genetic testing and three with clinical diagnosis (at least three clinical criteria but a negative genetic test) and 27 controls (13 females, 14 males, mean age 38.6 ± 19.6 years).

Results: Microscopic telangiectases were observed on the dorsum of the hands in 80/88 patients (91%): 77 with positive and three with negative genetic tests. No control showed vascular abnormalities. In six patients (7%), nailfold capillaroscopy showed pseudo-megacapillaries and megacapillaries; the remaining 82 (93%) and all controls, had normal capillaroscopic patterns.

Discussion: HHT can induce morphological changes in microcirculation that are more easily detectable on the dorsum of the hands than in the nailfold. Microscopic lesions without macroscopic telangiectases were also noted, suggesting the need for further research. Capillaroscopy may provide an additional non-invasive diagnostic criterion for HHT.

Introduction

Hereditary hemorrhagic telangiectasia (HHT), or Rendu-Osler-Weber disease, is an autosomal dominant disorder caused by mutations in the genes encoding for endoglin (chromosomal locus 9q34)1 or ALK-1 (12q1).2 The existence of an additional HHT-causing gene, which appears to be located on chromosome 5, has been hypothesized, but it has yet to be identified.3,4 According to a recent report, a subgroup of HHT individuals, with both familial HHT and juvenile polyposis, carry a germline mutation in the MADH4 gene.5 The prevalence of HHT is currently estimated at 1/8000.6,7 The disease is characterized by angiodysplastic lesions (telangiectases and arteriovenous malformations or AVMs), which can affect almost any organ, but primarily occur in the nose, skin of
the face, mouth, hands, gastrointestinal tract, liver, lungs and brain. Generally, spontaneous and recurrent epistaxis is the initial symptom, but it is not unusual for the onset of HHT to be characterized by life-threatening complications due to visceral involvement (haemothorax, haemoptysis, stroke, brain abscess). Generally, spontaneous and recurrent epistaxis is the initial symptom, but it is not unusual for the onset of HHT to be characterized by life-threatening complications due to visceral involvement (haemothorax, haemoptysis, stroke, brain abscess).

Cutaneous and mucosal telangiectases are small flat or raised lesions, bright red or purple in colour, composed of dilated and convoluted capillaries. Usually, they begin to appear on the skin within the third decade of life and tend to increase in size and in number with time, but they can be present in the nose much earlier, accounting for epistaxis in childhood and adolescence. Analysed the ultrastructure and three-dimensional (3-D) organization of these cutaneous lesions in HHT patients by means of skin biopsies and 3-D computer reconstruction. The earliest detectable lesion was a focal dilatation of post-capillary venules, which continued to enlarge and eventually conjoined to dilated arterioles through capillary segments. As the vascular lesion increased in size, these segments disappeared, leading to the formation of a direct arteriovenous communication.

Mucocutaneous microvascular involvement can also be investigated non-invasively by capillaroscopy, although to date, only a few studies have used this technique in the diagnosis of HHT. The nailfold area was used for observation, with the conclusion that capillaroscopy could be a useful tool in diagnosing this disease (‘giant loops’) and, in addition to physical examination and family history, could also assist in the differential diagnosis between the telangiectatic form of scleroderma and HHT.

The aim of our study was to examine the diagnostic role of nailfold capillaroscopy in HHT, and to assess the value of capillaroscopy in the diagnosis of this disease by examining the dorsal surface of the hands. To our knowledge, no data are available concerning microvascular abnormalities in this area. The choice to evaluate the dorsal surface of the hands was related to its accessibility and the facility of analysis, in a site which presents a consistent capillaroscopic pattern, visualized in all individuals as points or commas in the papillae, corresponding to the apex of the capillary loops.

Methods

Patients

From October 2001 to October 2004, a total of 109 patients with a clinically suspected diagnosis of HHT were referred to our University Interdepartmental Research Centre for Rendu-Osler-Weber disease. All were subjected to genetic counselling and molecular testing. According to the current international consensus criteria (family history, epistaxis, cutaneous or mucocutaneous telangiectases, or large visceral AVMs; at least three criteria are necessary for positive diagnosis), the diagnosis of HHT was established clinically in 103 (94.5%).

Genetic analysis permitted the identification of mutant genes on chromosomes 9 (ENG) and 12 (ALK-1) in 85/109 patients (55 ALK-1, 30 ENG). The disease-causing gene was excluded in 3/109 patients and has not yet been identified in 21/109 (in progress, possibly the hypothetical third gene).

Thus, the 88 patients (37 females, 51 males; mean age 39.7 ± 18.4 years, range 5–75) whose HHT diagnosis was definitively confirmed or excluded by genetic testing, considered as the gold standard for diagnosis, were enrolled in the study. The sample included 57 patients with the four aforementioned diagnostic criteria, and 25 with three diagnostic criteria. In 4/85 patients, only two diagnostic criteria were present (suspected HHT); all four had a first-degree family member affected with HHT, one had spontaneous epistaxis as the second criterion and three had AVMs. Two additional patients had only a positive family history (one criterion) (Table 1). The patients were divided into three groups: group 1 (16 patients aged 5–19 years), group 2 (28 patients aged 20–39 years), and group 3 (44 patients aged >40 years). A sample of 27 patients (13 females, 14 males; mean age 38.6 ± 19.6, range 7–71) whose epistaxis was due

<table>
<thead>
<tr>
<th>HHT diagnostic criteria</th>
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<tr>
<td>4 criteria</td>
<td>57</td>
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<tr>
<td>3 criteria*</td>
<td>n</td>
</tr>
<tr>
<td>A</td>
<td>9</td>
</tr>
<tr>
<td>B</td>
<td>6</td>
</tr>
<tr>
<td>C</td>
<td>8</td>
</tr>
<tr>
<td>D</td>
<td>2</td>
</tr>
<tr>
<td>2 criteria</td>
<td>4</td>
</tr>
<tr>
<td>1 criterion</td>
<td>2</td>
</tr>
<tr>
<td>Total</td>
<td>88</td>
</tr>
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</table>

*A, family history, epistaxis and visceral arteriovenous malformations (AVMs); B, epistaxis, telangiectases and AVMs; C, family history, epistaxis and telangiectases; D, family history, telangiectases and AVMs.
to other causes, such as rupture of blood vessels in the anterior septal area due to trauma, environmental desiccation or hypertension, were also recruited as a control group.

All patients and controls provided informed consent, and when the participant was <18 years of age, the written consent of a parent was obtained, despite the extremely non-invasive procedure.

Techniques

The skin microcirculation was examined in all participants with a Wild Heerbrugg-M650 microscope, and photographs of the investigated areas were taken using a Fuji S2-Pro camera. All examinations were performed by a single investigator (no inter-observer variability) who was unaware of the patient’s medical condition. The nailfold of all fingers (except thumbs, as the skin is thicker and microtraumas are more frequent than on the other fingers) and the dorsal surface of the hands corresponding to the thenar eminence (area of approximately 5 cm²) were investigated. The skin surface was studied with a fibre optic system, which emitted light at an angle of approximately 70° for optimal view; Vaseline oil was applied on the area to be examined to minimize the reflection from the skin surface and to visualize the capillaries underlying the cutaneous surface by light refraction. The capillaries were observed using a 6× to 16× magnification, which is appropriate for morphological studies. The examination began with a low magnification (6×) to obtain an overview over a larger area, and a 10–16× magnification permitted a satisfactory overall examination of the regional microcirculation morphology.

At the nailfold, the capillaries run parallel to the skin surface, and are visible as loops included in the dermal papillae, with an arterial (afferent) and a venous (efferent) limb connected by the apical segment. The arterial portion is normally more narrow (about 8 μm) than the venous portion (8–14 μm); the diameter of the joining apical part is 8–12 μm. In healthy people, the capillary pattern is usually characterized by loops regularly aligned, hairpin shaped, with a regular calibre without dilatations which occupy the observed field with homogeneous density. The subpapillary vascular plexus is visible in only 30% of individuals, and is relatively unimportant, clinically speaking. Morphological parameters evaluated were: visibility, morphology and loop direction; capillary density; enlarged loops; megacapillaries; microhaemorrhages; avascular areas; neo-angiogenesis phenomena.

The capillaries of the dorsal skin of the hands have an uniform appearance in healthy subjects, and are uniformly distributed over the field of vision and dermal papillae, irrespective of age and sex. Their longitudinal axis is perpendicular to the skin surface and only the apex of the capillary loops can be visualized as points or commas in the papillae. Normally, the subpapillary vascular plexus is not apparent.

Statistics

The sensitivity, specificity, predictive value and diagnostic accuracy of the classical diagnostic criteria (epistaxis, telangiectasia and positive family history) with and without the capillaroscopic pattern (possible microvascular abnormalities) were evaluated. Such parameters were computed as follows and then expressed as percentages when discussing the results: sensitivity (the probability that the screening test is positive given that the person has the disease); specificity (the probability that the screening test is negative because the subject does not have the disease); positive predictive value (PPV, the probability that a person with a positive test result has the disease); negative test predictive value (NPV, the probability that a person with a negative test result does not have the disease); diagnostic accuracy (the probability of a true diagnosis; true positives plus true negatives divided by total numbers).

Results

In 6/88 patients (7%), the nailfold examination showed pseudo-megacapillaries and megacapillaries (diameters up to 25 and 40 μm, respectively) between capillaries of normal shape and size (Figure 1). In the remaining 82 patients (93%), the capillaroscopic pattern was normal: loops were regularly aligned without morphological alterations or with light and non-specific anomalies (loop enlargement in the efferent, apical, and/or afferent and efferent part in eight patients aged >50 years). No vascular anomalies were found in the healthy subjects (Figure 2).

Microvascular abnormalities were observed on the dorsal skin of the hands in 80/88 patients (91%), including 77/80 with positive genetic testing and 3/80 with negative genetic testing; the morphologic changes were easily distinguished from the pattern of controls (no anomalies, Figure 3). This abnormal pattern was observed in 13/16 (81%) in group 1, in 27/28 (96%) in group 2, and in 40/44 (91%) in group 3 (Table 2). Three different types of alterations could be distinguished and were classified as
follows: (i) segmental/truncal telangiectases (short linear dilated vessels which in some cases were tortuous or serpiginous, Figure 4a); (ii) plexiform/reticular telangiectases (ectasic vessels disposed in a reticulated structure, Figure 4b); and (iii) saccular telangiectases (sacciform ektasias, Figure 4c).

Table 2 Capillaroscopic examination of the dorsal surface of the hands (88 patients, 27 controls)

<table>
<thead>
<tr>
<th>Patients</th>
<th>Telangiectases</th>
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<tbody>
<tr>
<td>All patients (n=88)</td>
<td>80 (91%)</td>
</tr>
<tr>
<td>Group 1 (n=16)</td>
<td>13 (81%)</td>
</tr>
<tr>
<td>Group 2 (n=28)</td>
<td>27 (96%)</td>
</tr>
<tr>
<td>Group 3 (n=44)</td>
<td>40 (91%)</td>
</tr>
<tr>
<td>Controls (n=27)</td>
<td>0 (0%)</td>
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</tbody>
</table>

Group 1, patients aged 5–19 years; group 2, 20–39 years, group 3, 40–75 years.
These different types of telangiectases were variously associated in 26 patients (32.5%), isolated in 54 (67.5%), segmental/trunkal in 32/3 patients, respectively, and reticular/saccular in 15/4 patients. They were not visible with the naked eye. The microscopic lesions were associated with macroscopic telangiectases in 59/80 patients (74%) which were located on lips, tongue, palate, face, trunk, arms and pulps of the fingers. In 26/88 patients (30%), no cutaneous telangiectases were found on routine inspection, but the otolaryngologist found the typical lesions in 13 of these 26 using rhinoscopy.

Capillaroscopic examination was negative in 8/85 HHT patients (9%), three of whom presented skin lesions visible to the naked eye; these patients had severe anaemia (Hb 5.0, 5.1 and 5.7 g/dl, respectively) due to recurrent epistaxis requiring blood transfusions. There were no false positives in the control group.

When microvascular abnormalities were used as a third criteria for a definite diagnosis of HHT, the sensitivity, PPV and the diagnostic accuracy increased from 74%, 95% and 72%, using only the three clinical signs to 90%, 96% and 86%, respectively, using at least two clinical signs together with microscopic lesions of the dorsal skin of the hand (63/88 vs. 76/88 patients). Using both methods (three clinical signs or two clinical signs plus capillaroscopic pattern), we obtained 97% sensitivity, 97% PPV and 93% accuracy (see Table 3).

**Discussion**

Capillaroscopy has been used extensively, both in clinical practice and research, to study phenomena in the skin microcirculation, mainly in the nailfold of fingers and toes, where a large portion of the capillary loop can be observed. The technique is currently used for the assessment of patients with connective tissue disorders but it is also useful in many other diseases, including hypertension, diabetes mellitus, arterial and venous diseases, and skin disorders. Microscopic investigation of the dorsal skin of the hands is an easily performed, non-invasive examination that is safe, inexpensive and comfortable for the patient.

Previous studies have revealed abnormal morphological nailfold capillary changes that were believed to be characteristic of HHT. Maire (1986, fluorescence videomicroscopy) found giant capillaries (diameter up to 150 μm) between capillaries of normal shape and size, and concluded that capillaroscopy contributed to differential diagnosis of the telangiectatic forms of scleroderma and Osler’s disease. Mager (2000) found giant loops involving the entire visible capillary field imperceptible to the naked eye in 45/58 patients (83%), concluding that capillary microscopy can be a valuable tool in diagnosing HHT.

In our experience, capillaroscopy allowed detection of vascular abnormalities of the nailfold capillary bed (pseudo-megacapillaries and megacapillaries whose diameters were about 25 and 40 μm, respectively) in only six patients (7%), while in the remaining patients, the capillaroscopic nailfold pattern was normal, or characterized only by slight and non-specific anomalies in patients with clinical manifestations of HHT. These latter alterations may also be present in healthy persons whose capillaries have become slightly dilated or tortuous with age. Thus the finger nailfold did not present a particularly appropriate site for microscopic investigation, and nailfold capillaroscopy did not offer much support in establishing the diagnosis of HHT.

However, the abnormalities detected on the dorsum of the hands indicate that skin microcirculation may be both affected by HHT and subject to investigation by capillaroscopy. As in other diseases, cutaneous microvascular abnormalities in HHT are more evident in the dorsum of the hands rather than elsewhere, as this location offers a more extensive surface (5 cm²) for examination, thereby increasing the possibility of lesion detection compared to the nailfold (1–2 cm²). Microscopic lesions were detected in 80/88 (91%) of our patients, including 77/88 (87.5) with positive genetic tests and 3/88 with negative genetic tests (Table 2). Moreover, 59 patients had microscopic skin telangiectases together with cutaneous telangiectases visible to the naked eye; 21 individuals had only microscopic anomalies. Therefore, the microscopic features revealed by capillaroscopy

<table>
<thead>
<tr>
<th>All diagnostic criteria*</th>
<th>Two criteria plus microvascular abnormalities</th>
<th>Both methods</th>
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<tr>
<td><strong>Sensitivity</strong></td>
<td>74%</td>
<td>90%</td>
</tr>
<tr>
<td><strong>PPV</strong></td>
<td>95%</td>
<td>96%</td>
</tr>
<tr>
<td><strong>Accuracy</strong></td>
<td>72%</td>
<td>86%</td>
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*Epistaxis, telangiectasia and positive family history. PPV, positive predictive value.
may provide an additional cutaneous diagnostic criterion for HHT diagnosis.

Advances in the field of genetics have permitted the identification of many gene mutations, facilitating the characterization of different members of the same family at risk for disease. Molecular diagnosis can identify subjects who have or have not inherited the mutation, thereby avoiding the performance of unnecessary instrumental analyses for non-carriers. Unfortunately, genetic heterogeneity still hinders the genetic diagnosis in all patients with suspected HHT, as it remains difficult to highlight all possible genetic mutations. Furthermore, molecular genetic testing requires specialized centres and teams of experts, in addition to considerable financial support. Until molecular diagnostic testing becomes universally available, the diagnosis of HHT remains clinical, and the detection of a third criterion is required for a definite analysis. Detection of capillaroscopic abnormalities might help to provide the necessary criteria for definite diagnosis, and could assist in selecting patients who should be further evaluated more invasively (computed tomography, magnetic resonance imaging, endoscopy, etc.) for eventual visceral involvement. These procedures could be also reserved for patients with a definite HHT diagnosis, to permit prompt control of associated visceral malformations (embolization of pulmonary and cerebral arteriovenous malformations, laser photocoagulation of gastrointestinal telangiectases), which can lead to increased mortality when left untreated.

HHT displays an age-related penetrance, which renders the diagnosis difficult in younger patients, and occasionally individuals inheriting the gene do not demonstrate it phenotypically, or present symptoms so slight as to remain unnoticed for many years. Patients with only microscopic lesions at first may develop macroscopic telangiectases later in life (Table 2). In addition, it is not known whether, with age, microscopic lesions might become visible with the naked eye; further studies are necessary to clarify this question.

Our findings demonstrate that HHT can induce morphological changes in the skin microcirculation that can be easily detected by capillaroscopic examination of the dorsal surfaces of the hands. The presence of microscopic lesions without macroscopic telangiectases suggests the need for further research of these anomalies, as microscopic telangiectases could be regarded as an additional diagnostic feature and added to the screening protocol for HHT patients.

References


