Value of Capillary Microscopy in the Diagnosis of Hereditary Hemorrhagic Telangiectasia

Johannes J. Mager, MD; Cornelius J. J. Westermann, MD, FCCP, PhD

Background: Hereditary hemorrhagic telangiectasia (HHT) is a hereditary disorder, leading to easily bleeding telangiectases on the skin and mucosal surfaces. The disease is associated with arteriovenous malformations in multiple organs. Potentially serious complications warrant an early diagnosis. Telangiectases are the hallmark of the disease, but may be difficult to distinguish.

Objectives: To evaluate the value of capillary microscopy in the diagnosis of HHT and to compare the capillary pattern of the fingernail folds in patients with HHT and healthy persons.

Setting: Outpatient department of a general hospital.

Participants: A random sample of 54 patients with HHT and a volunteer sample of 40 healthy persons.

Main Outcome Measure: The difference in the capillary pattern between patients with HHT and healthy volunteers.

Results: Forty-five (83%) of 54 patients with HHT had giant loops between the normal capillaries in the nail fold. Two patients had only enlargement of the draining limb of the capillary. Seven patients (13%) had no vascular abnormalities in the nail fold. Seven of 9 patients with HHT but without cutaneous telangiectases had microvascular abnormalities. None of the volunteers had vascular abnormalities. The difference between both groups was significant ($\chi^2$, $P<.001$).

Conclusion: Capillary microscopy can be a valuable tool in diagnosing HHT.

Arch Dermatol. 2000;136:732-734

HEREDITARY hemorrhagic telangiectasia (HHT), also known as Osler-Weber-Rendu syndrome, is an autosomal dominant disease with an age-related penetrance. The disease is characterized by vascular anomalies, which may develop in virtually any organ. The prevalence varies and may approach 1 in 10 000 in specific regions. Linkage studies have identified at least 3 HHT loci, on chromosomes 9, 12, and elsewhere. The mutated genes on chromosomes 9 and 12 encode respectively for endoglin and activin receptor–like kinase 1, both transmembrane proteins expressed on endothelial cells. Activin receptor–like kinase 1, which is a type 1 receptor for transforming growth factor β (TGF-β), can bind both TGF-β1 and activin A. Endoglin exhibits high-affinity binding of TGF-β1 and TGF-β3, which are involved in angiogenesis and in vessel maturation. They are also part of an interplay between cells, matrix, and external factors in responding to vascular insults.

Clinical manifestations of HHT include mucocutaneous telangiectases that bleed easily, recurrent epistaxis, and larger arteriovenous malformations in parenchymous organs. The most common site for arteriovenous malformations is the lung; these malformations are dangerous, particularly because they are associated with paradoxical, sometimes septic, emboli. A rarer but equally serious complication is hemoptysis or hemothorax. These potentially serious complications warrant early diagnosis. At present, a genetic diagnosis is possible in only a few families. A definite clinical diagnosis of HHT is based on family history and the presence of telangiectases or arteriovenous malformations. Telangiectases are the hallmark of the disease, but they usually start to appear in the third decade of life, may be subtle, and are sometimes difficult to distinguish from cherry angiomas or venectasia. The HHT Foundation International has recently arrived at a consensus about requiring a minimal number of 3 typical telangiectases for the diagnosis of HHT. When only 1 or 2 telangiectases are found, the diagnosis is uncertain. This was the case in 6 of 98 screened adult family members in a study performed by Haitjema et al. In patients with 1 or 2 telangiectases, it is not clear whether a search for arteriovenous malformations should be done. In such cases, capillary microscopy of the nail fold could be valuable if addi-
PATIENTS AND METHODS

We studied 54 patients (25 male and 29 female) with a definite clinical diagnosis of HHT. The mean age of the patients was 43 years (age range, 6-81 years). Sixteen patients were 6 to 29 years old (group 1), 21 were 30 to 50 years old (group 2), and 17 patients were older than 50 years (group 3). We also studied 40 healthy persons (18 male and 22 female) as controls. Their mean age was 40 years (age range, 9-74 years). Age and sex distributions in patients with HHT and normal controls were matched. We could not perform the investigation in blind conditions, because many of the patients had visible telangiectases.

We investigated the nail folds of all fingers, except both thumbs, because the skin at the nail fold of the thumb may be too thick for adequate inspection. We used a stereozoom microscope (Wild M3Z; Leica AG, Heerbrugg, Switzerland) and immersion oil to increase the transparency of the skin. We used magnifications of ×16 to ×40 to inspect the capillaries. The light source was elicited by 2 arms of fiber optics, each making a 45° angle with the nail fold surface.

We used the χ² test to compare the results in the different groups.

Results of Capillary Microscopy in 54 Patients With Hereditary Hemorrhagic Telangiectasia and 40 Controls

<table>
<thead>
<tr>
<th>Age Range of Patients, y</th>
<th>No. (%) of All Patients</th>
<th>Controls</th>
</tr>
</thead>
<tbody>
<tr>
<td>16-29</td>
<td>12 18 15</td>
<td>45 (83) 0</td>
</tr>
<tr>
<td>30-50</td>
<td>2 0 0</td>
<td>2 (4) 0</td>
</tr>
<tr>
<td>51-81</td>
<td>2 3 2</td>
<td>7 (13) 40</td>
</tr>
</tbody>
</table>

The Table shows the results of our study. The afferent and draining limbs of the capillary loops can be identified by the direction of the blood flow. In addition, the draining limbs tend to be thicker than the afferent limbs. Sometimes, even flowing erythrocytes can be seen. In healthy persons, capillaries are normally hairpin shaped, but they may have a twisted or slightly tortuous configuration, especially in elderly persons. Figure 1 shows a normal capillary pattern at the nail fold with a homogeneous distribution. The 2 limbs of the capillaries run a more or less parallel course. The subpapillary venous plexus is vaguely visible proximal to the capillaries.

In 45 (83%) of 54 patients with HHT, we observed one or more giant loops. In some patients, these loops had a tortuous configuration (Figure 2). The giant loops involve the entire visible capillary and are often single between normal capillaries. The draining limbs are usually more enlarged than the afferent limbs. The abnormal vascular configurations had not been noted before the microscopic examination and afterwards were not visible or were barely visible with the naked eye.

In 2 patients, we observed a more moderate variation, which consisted of enlargement of the draining limb between normal capillaries. The postcapillary venules and subpapillary venous plexus are visible proximal to the capillaries.

We investigated the nail folds of all fingers, except both thumbs, because the skin at the nail fold of the thumb may be too thick for adequate inspection. We used a stereozoom microscope (Wild M3Z; Leica AG, Heerbrugg, Switzerland) and immersion oil to increase the transparency of the skin. We used magnifications of ×16 to ×40 to inspect the capillaries. The light source was elicited by 2 arms of fiber optics, each making a 45° angle with the nail fold surface.

We used the χ² test to compare the results in the different groups.
capillary (Figure 3). In 7 patients (13%), there were no vascular abnormalities. There was no significant difference in the results between groups 1 and 3 ($\chi^2, P = .32$) and 2 and 3 ($\chi^2, P = .81$). Nine patients had no macroscopic cutaneous telangiectases, but 5 of the 9 had giant loops and 2 had enlargement of draining limbs. None of the control subjects had vascular abnormalities in the capillary pattern of the nail fold, except for one of the older control subjects, who had some local puicities in the distribution pattern. The difference between the patients with HHT and the normal controls was highly significant $\chi^2, P<.001$.

We observed microvascular abnormalities in 47 (87%) of the 54 patients with HHT by investigating the nail folds of 8 fingers. This finding indicates a sensitivity and specificity of capillary microscopy of 87% and 100%, respectively, provided that the patients do not have a connective tissue disease. The exact sensitivity and predictive value remain unclear, however, because all patients had clinical manifestations of HHT. These clinical manifestations are at present still required for the diagnosis of this genetic disease. Apart from a family history of HHT, telangiectases or arteriovenous malformations, with or without epistaxis, are required for the diagnosis. Future research, when a genetic diagnosis is possible in large numbers of patients, will disclose the true sensitivity and predictive value. In addition, HHT displays an age-related penetrance, with progression of telangiectases with aging. This progression with aging means that patients with normal microscopic findings might develop microvascular abnormalities with aging. The giant loops can be regarded as microscopic telangiectases, which are the major criterion for the diagnosis of HHT. They may resemble those in scleroderma, but the latter occur in a disarranged capillary pattern. Hereditary benign telangiectasia, which is also primary telangiectasia of childhood, could also be associated with microvascular abnormalities, possibly with giant loops as well. We did not examine patients with this benign condition. Such patients, however, would have a different family history, because the lesions fade with age.

The diagnosis of HHT may be difficult because of few or atypical telangiectases. This is the case particularly in young patients, because telangiectases usually start to appear at an adult age. Our results show that capillary microscopy can be useful in these patients, because additional microscopic telangiectases were found. Moreover, in 7 of 9 patients without macroscopic cutaneous telangiectases, capillary microscopy disclosed abnormal blood vessels. We did not examine the toes, because they are rarely involved in HHT. The giant loops are very obvious. Enlargement of the draining capillary limbs requires more careful inspection. Capillary microscopy is a simple noninvasive and inexpensive procedure and takes only a few minutes to perform. Microvascular abnormalities in HHT seem to begin with dilatation of postcapillary venules, which drain several capillaries. This pathogenesis explains the prominent enlargement of the draining limbs, but it is remarkable that we often observed only 1 affected capillary between normal neighbor capillaries.

Accepted for publication July 22, 1999.

This study was supported in part by the Janivo Foundation, Zeist, by the Mr Willem Bakhuis Roozeboom Foundation, Amsterdam, and by Glaxo Wellcome, Zeist, the Netherlands.

The authors thank Cornelis G. Ramselaar, MD, PhD, for his thoughtful review of the manuscript.

Reprints: Cornelius J.J. Westermann, MD, FCCP, PhD, Department of Pulmonary Disease, St Antonius Hospital, Postbus 2500, 3430 EM Nieuwegein, the Netherlands.

References

11. White RI. Second HHT scientific meeting. HHT Found Int Direct Connection. 1998; 2, P= .81). Nine patients had no macroscopic cutaneous telangiectases, but 5 of the 9 had giant loops and 2 had enlargement of draining limbs. None of the control subjects had vascular abnormalities in the capillary pattern of the nail fold, except for one of the older control subjects, who had some local puicities in the distribution pattern. The difference between the patients with HHT and the normal controls was highly significant $\chi^2, P<.001$.

Figure 3. Enlargement of a draining limb and postcapillary venule (in a female of African descent).