Hereditary Hemorrhagic Telangiectasia

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Disclosures

- I have no actual or potential conflict of interest to disclose in relation to this presentation.
Outline

▪ HHT refresher

▪ Clinical manifestations, screening, and treatment

▪ How does this impact your practice?

▪ What’s new in HHT
Refresher: what is HHT?

- Osler-Weber-Rendu
- Inherited disorder of blood vessel formation
- Mucocutaneous telangiectasias and visceral arteriovenous malformations
- Manifestations depend on tissue distribution
HHT is NOT…

- A coagulopathy
- Von Willebrand Disease
- Platelet disorder
- Other multi-eponymous diseases
- … as rare as you might think
Genetics

- Autosomal dominant inheritance
- Affects up to 1:5000 worldwide
- More prevalent than most realize
  - Fragile X (1:5000)
  - Marfan (1:5,000 to 10,000)
  - Myasthenia gravis (1:4000)
## Diagnostic criteria

<table>
<thead>
<tr>
<th>Level of Diagnostic Certainty</th>
<th>Number of Criteria Present</th>
</tr>
</thead>
<tbody>
<tr>
<td>Unlikely</td>
<td>≤ 1</td>
</tr>
<tr>
<td>Possible</td>
<td>2</td>
</tr>
<tr>
<td>Definite</td>
<td>≥ 3</td>
</tr>
</tbody>
</table>

1. Recurrent spontaneous epistaxis
2. Multiple characteristic telangiectasias
3. Visceral arteriovenous malformations
4. Family history meeting above criteria
Genetics

- Autosomal dominant inheritance
- Affects up to 1:5000 worldwide
- More prevalent than most realize
  - Fragile X (1:5000)
  - Marfan (1:5,000 to 10,000)
  - Myasthenia gravis (1:4000)
Clinical manifestations

- Mucocutaneous telangiectasis
  - Face, lips, ears, finger tips
  - Nasal and GI mucosa

- Visceral AVMs
  - Lungs, brain, liver, elsewhere
Clinical manifestations
Epistaxis

- Affects almost all patients
  - Nearly 100% by age 40
- Average onset age 12
- Symptoms range from occasional epistaxis to life-threatening hemorrhage
- Anemia is common
Clinical manifestations
GI telangiectasias

- Present in most patients with HHT
- Clinically significant GI bleeding in 10%
- Most common in stomach and small bowel
Clinical manifestations
Hepatic vascular malformations

- Common in patients with HHT
- Typically cause no symptoms (10%)
- Manifestations depend on predominant shunting
  - HA -> HV (arteriovenous)
  - HA -> PV (arterioporal)
  - PV -> HV (portovenous)
- High output heart failure, portal hypertension, biliary ischemia, encephalopathy
Clinical manifestations
Cerebral Vascular Malformations

- Affect up to 10% with HHT
- AVMs and pial fistulae at highest risk of bleeding
  - 0.5% per year
- Small AVMs, capillary telangiectasias, venous anomalies less likely to bleed
Pulmonary AVMs

Diffuse (A), simple (B), and complex (C) pulmonary AVM morphologies, from Trerotola et al., AJR 2010; 195:383.
Pulmonary AVMs:
Clinical consequences and complications

• Right-to-left intrapulmonary shunt
  • Hypoxemia
  • Paradoxical embolic complications
    • Embolic stroke; brain abscess
• Hemorrhage
Pulmonary AVMs: Right to left shunt
Pulmonary AVMs

Pulmonary capillary filtration

Pulmonary AVMs:
Embolic complications

Embolic stroke and transient ischemic attacks
- Clinical stroke diagnosed in 25% with PAVMs
- 50% will show infarcts on brain imaging

Brain abscess
- 400-fold more likely with PAVM (10%)
- Often occur before HHT / PAVM diagnosis
- Periodontal microbes

Other
- Coronary embolus, vertebral abscess, others
Relevance to your practice
Overlap with common IM conditions

- Unexplained anemia
- GI bleeding
  - Melena may triggers search for colon cancer
  - Angioectasias from other conditions
- Stroke
- Heart failure
- Pulmonary hypertension
Interim Summary

- HHT is not very rare
- Manifestations are often easily recognizable
- Recognition allows effective treatment
- Overlap with common medical conditions
Updates…

1. Better understanding of molecular pathogenesis

2. Advances in treating epistaxis

3. Advances in embolotherapy for lung AVMs

4. Inhibitors of angiogenesis
## Update #1
**Advances in understanding pathogenesis**

<table>
<thead>
<tr>
<th>Gene</th>
<th>Name</th>
<th>Phenotype</th>
<th>Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>Endoglin</td>
<td>HHT-1</td>
<td>Epistaxis, lung, brain AVMs</td>
<td>45%</td>
</tr>
<tr>
<td>ACVRL1</td>
<td>HHT-2</td>
<td>Epistaxis, liver and GI AVMs</td>
<td>40%</td>
</tr>
<tr>
<td>Smad4</td>
<td>HHT-Juvenile polyposis syndrome</td>
<td>HHT plus juvenile polyposis</td>
<td>2%</td>
</tr>
<tr>
<td>Unknown gene, chromosome 5</td>
<td>HHT-3</td>
<td>Same as HHT-1</td>
<td>&lt; 8%</td>
</tr>
<tr>
<td>Unknown gene, chromosome 7</td>
<td>HHT-4</td>
<td>Epistaxis, CVMs, PAVMs</td>
<td></td>
</tr>
<tr>
<td>GDF2</td>
<td>HHT-5</td>
<td>Similar to HHT-2</td>
<td>&lt; 5%</td>
</tr>
<tr>
<td>RASA1</td>
<td>Capillary malformation-AVM syndrome; Parkes Weber</td>
<td>Cutaneous telangiectasia, visceral AVMs (muscle, bone, spine, brain)</td>
<td>NA</td>
</tr>
<tr>
<td>EPHB4</td>
<td>CM-AVM2</td>
<td>Cutaneous telangiectasia, CNS AVMs, epistaxis</td>
<td>NA</td>
</tr>
</tbody>
</table>
Endothelial TGF-beta signaling
Advances in treating epistaxis
NOSE Study

Figure 2. Change in Epistaxis Severity Score With Topical Endonasal Therapy in the North American Study of Epistaxis in HHT

Advances in treating epistaxis

Coblation

- Ablation of nasal telangiectasis
  - Electrocautery -> laser -> coblation
- Less thermal injury (70°C vs 600°C)
- More sustained control of epistaxis
  - 24+ months sustained response
  - No difference with bevacizumab injection

Advances in embolotherapy
Advances in embolotherapy


Inhibitors of angiogenesis
Bevacizumab

- Monoclonal Ab vs vascular endothelial growth factor (VEGF)
- Developed for treatment of advanced solid tumors
  - Colorectal, lung, others
- Function
  - Promotes angiogenesis
  - Stabilizes vascular endothelial cell
  - Cross talk with TGF-beta pathway
Bevacizumab in patients with HHT and severe hepatic vascular malformations and high cardiac output

**Figure 1.** Blinded Cardiac Index Before Treatment and 3 and 6 Months After the Beginning of Treatment With Bevacizumab

Cardiac index significantly declined in response to bevacizumab treatment. Squares indicate mean values; error bars, 95% CIs; boxes, median and interquartile range; shaded area, reference value range.

JAMA, 2012: 307(9):950-955
Bevacizumab in patients with HHT and severe hepatic vascular malformations and high cardiac output

**Figure 3.** Epistaxis and Hemoglobin Levels After Treatment With Bevacizumab

The mean duration of epistaxis episodes (measured as minutes per month) significantly declined; the mean number of epistaxis episodes was 26 episodes per month before treatment and 20 per month after treatment. Hemoglobin levels remained stable throughout the course of the study. Squares indicate mean values; open circles, individual values; error bars, 95% CI; and filled circles, outliers (either an outside value, defined as a value smaller than the lower quartile minus 1.5 times the interquartile range, or larger than the upper quartile plus 1.5 times the interquartile range; or a far-out value, defined as a value that is smaller than the lower quartile minus 3 times the interquartile range, or larger than the upper quartile plus 3 times the interquartile range). P values are for mixed model.
Intravenous bevacizumab for refractory HHT-related epistaxis and GI bleeding

### TABLE 3. ESS Scores in Patients With Significant Epistaxis (n = 30)

<table>
<thead>
<tr>
<th>Variable</th>
<th>Baseline</th>
<th>During the initial bevacizumab treatment cycle</th>
<th>After the completion of the initial treatment cycle</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>1 mo</td>
<td>3 mo</td>
</tr>
<tr>
<td>n</td>
<td>30</td>
<td>21</td>
<td>14</td>
</tr>
<tr>
<td>ESS score</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean ± SD</td>
<td>6.6±2.2</td>
<td>3.9±2.1</td>
<td>4.4±1.8</td>
</tr>
<tr>
<td>Median (25th, 75th)</td>
<td>6.5 (5.2, 8.2)</td>
<td>3.3 (2.4, 5.4)</td>
<td>4.0 (3.2, 6.0)</td>
</tr>
<tr>
<td>Change from baseline</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean ± SD</td>
<td></td>
<td>-2.9±2.9</td>
<td>-2.4±3.0</td>
</tr>
<tr>
<td>Median (25th, 75th)</td>
<td></td>
<td>-3.3 (-4.2, -1.5)</td>
<td>-2.8 (-5.4, -0.8)</td>
</tr>
<tr>
<td>P value (signed-rank test)</td>
<td></td>
<td>&lt;.001</td>
<td>.013</td>
</tr>
</tbody>
</table>

ESS = Epistaxis Severity Score.

### TABLE 4. Blood Transfusion Data Before and After Bevacizumab Treatments

<table>
<thead>
<tr>
<th>Variable</th>
<th>Before bevacizumab treatment</th>
<th>After the initiation of bevacizumab treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Lifetime</td>
<td>6 mo (1-3 mo and 4-6 mo)</td>
</tr>
<tr>
<td>All patients (N=34)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Number followed</td>
<td>34</td>
<td>34</td>
</tr>
<tr>
<td>Any transfusion, n (%)</td>
<td>28 (82)</td>
<td>18 (53)</td>
</tr>
<tr>
<td>RBC units, median (min, max)</td>
<td>9.5 (1.1-500)</td>
<td>9 (1.96)</td>
</tr>
<tr>
<td>Non-transfusion-dependent patients (n=18)</td>
<td>18</td>
<td>18</td>
</tr>
<tr>
<td>Number followed</td>
<td>12 (67)</td>
<td>2 (11)</td>
</tr>
<tr>
<td>RBC units, median (min, max)</td>
<td>2.5 (1, 10)</td>
<td>1 (1.1)</td>
</tr>
<tr>
<td>Transfusion-dependent patients (n=16)</td>
<td>16</td>
<td>16</td>
</tr>
<tr>
<td>Number followed</td>
<td>16 (100)</td>
<td>14 (88)</td>
</tr>
<tr>
<td>RBC units, median (min, max)</td>
<td>75 (4, 500)</td>
<td>12 (1.96)</td>
</tr>
</tbody>
</table>

*RBC = red blood cell.

+P <.007 (McNemar’s test) comparing the 6-mo interval before bevacizumab treatment with a similar 6-mo interval after the completion of the initial bevacizumab treatment (7-12 mo) for the overall cohort as well as transfusion-dependent cohort.

*The median (min, max) number of RBC units transfused is presented for the subset of patients who received transfusions.

Mayo Clin Proc, 2018; 93(2):155-166
Intravenous bevacizumab for refractory HHT-related epistaxis and GI bleeding

FIGURE 2. Improved mucocutaneous telangiectasias after IV bevacizumab treatment. IV = intravenous.
Intravenous bevacizumab for refractory HHT-related epistaxis and GI bleeding

Unanswered questions:

- Length/frequency of treatment
- Adverse effects, especially after decades of use
- Precise mechanism?
- Alternatives
What does the future hold?

• Increased awareness will prevent complications
• Improvements in existing screening and treatment
• Expanding role of inhibitors of angiogenesis
• Alternates to bevacizumab
  • Thalidomide, Pomalidomide, Pazopinib, others
• HHT is not so rare
• Clinical manifestations are easily recognizable
• Complications can be effectively prevented
• Defects in genes in endothelial TGF-beta signaling
• Recent improvements in treating epistaxis, PAVMs
• Inhibitors of angiogenesis have revolutionized HHT treatment