Rendu Osler Weber disease or Hereditary Hemorrhagic Telangiectasia (HHT): liver vascular involvement

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VALDIG European Group

VASCERN, the European Reference Network on Rare Multisystemic Vascular Diseases

• Italian HHT Foundation “Onilde Carini”
HHT: genetics & epidemiology

<table>
<thead>
<tr>
<th>HHT</th>
<th>chromosome</th>
<th>protein</th>
</tr>
</thead>
<tbody>
<tr>
<td>HHT1</td>
<td>9</td>
<td>endoglin</td>
</tr>
<tr>
<td>HHT2</td>
<td>12</td>
<td>ALK1</td>
</tr>
<tr>
<td>HTJP</td>
<td>18</td>
<td>Smad4</td>
</tr>
<tr>
<td>HHT3</td>
<td>5</td>
<td>/</td>
</tr>
<tr>
<td>HHT4</td>
<td>7</td>
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</tr>
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</table>

- 1/5,000 people worldwide have this disorder
- autosomal dominant
- complete penetrance by the age of 40

HHT: pathogenesis

Abnormality of vascular structure
(and normal coagulation!)

Anomalous arterio-venous connection
which can present as:

Teleangiectases in superficial vessels
Visceral vascular malformations (lung, liver, brain,...)
Teleangiectases in HHT
Teleangiectases in HHT
Teleangiectases in HHT
Vascular malformations (VMs) in HHT

VM = Anomalous vascular connection (artery/ies to vein/s, vein-to-vein)

If ArterioVenous:
Upstream and downstream hemodynamic consequences
## HHT: clinical diagnosis

### Curacao criteria


<table>
<thead>
<tr>
<th>Criteria</th>
<th>Description</th>
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</thead>
<tbody>
<tr>
<td>Epistaxis</td>
<td>Spontaneous and recurrent</td>
</tr>
<tr>
<td>Telangiectases</td>
<td>Multiple, at characteristic sites: lips, oral cavity, fingers, nose</td>
</tr>
<tr>
<td>Visceral lesions</td>
<td>GI Telangiectasia, pulmonary, hepatic, cerebral or spinal AVMs</td>
</tr>
<tr>
<td>Family history</td>
<td>A first degree relative with HHT according to these criteria</td>
</tr>
</tbody>
</table>

**HHT definite** = 3 or more criteria

**HHT suspected or likely** = 2 criteria

**HHT unlikely** = 0 or 1 criterion

*genetic testing on a clinical basis*
Vascular malformations (VMs) in HHT: “the great masquerader”

...cerebral abscess, melena, cardiac failure, ascites, stroke, liver mass .....
Liver VMs in HHT: epidemiology

data from series including consecutively subjects with suspected or definite HHT

Liver VMs in HHT: 41-70% of HHT patients, prevalence in general non-HHT population: 1/7,000-1/12,000

Liver VMs are more frequent in HHT2 than in HHT1

mostly women: male/female ratio 1:4

mean age at diagnosis 46-52

Buscarini E, Ultrashall Med 2004
Stabile Ianora A, Radiology 2004
Buscarini E, DDS 2011
Singh S, J Hepatol 2014
Liver VMs in HHT: pathophysiology

Liver involvement in HHT is defined by the presence of VMs potentially involving all hepatic vessels.

At earliest stage vascular derangement is represented by diminutive telangiectases scattered throughout liver parenchyma and visible also on liver surface.
Liver VMs in HHT: pathophysiology

Progressive overload of hepatic veins > cardiac and circulatory overload > high output cardiac failure

Progressive overload of portal vein/mesenteric circulation > portal hypertension

Liver parenchyma > focal nodular hyperplasia, nodular regenerative hyperplasia

Biliary tree (flow steal) > cholestasis, ischemic cholangitis

Mesenteric vessels (flow steal) > mesenteric ischemia

Veno-venous shunts > encephalopathy
Doppler US is sufficiently accurate and suitable for first-line imaging of the liver in the general HHT population

NO liver biopsy: unnecessary for diagnosis of liver VMs and risk of bleeding

Consensus Recommendations, Liver Int, 2006
International HHT Guidelines, J Med Genet 2011
AISF Guidelines, Vascular disorders of the liver, 2011
EASL Guidelines, Vascular diseases of the liver, 2016
Liver VMs in HHT: diagnosis clinical features outcome management

**NO CEUS:** unnecessary, possibly harmful

**NO clinical elements/scores:** no guesswork when sensitive imaging available

Schelker RC, WJG 2017
Singh S, J Hepatol 2014
Severity grading of liver VMs

Buscarini E et al. AJR 1994, Ultraschall Med 2004

grade 0+

grade 1

grade 2
Severity grading of liver VMs

Buscarini E et al. AJR 1994, Ultraschall Med 2004
Screening protocol for liver VMs

- clinical, laboratory (LFTs), genetic, and instrumental assessment:
  - Doppler US
  - Echocardiography (cardiac index, RV systolic pulmonary artery pressure)
  - If needed: GI endoscopy, radiologic evaluations (chest/abdomen: MR, CT, scintigraphy, angiography), right heart cath, HVPG
Liver involvement is generally asymptomatic BUT it can entail significant morbidity/mortality

High output cardiac failure (HOCF)
Portal hypertension complications
Ischemic cholangitis

in 30% anicteric cholestasis (GGT>ALP)
normal Albumin, INR

Garcia-Tsao G, NEJM 2000;
De Leve LD, Hepatology 2009
Buscarini E, J Hepatol 1997; Dig Liv Dis 2005; Dig Dis Sci 2011
EASL Guidelines, Vascular diseases of the liver, 2016
How many HHT pts with liver VMs develop symptoms?

8% = proportion of symptomatic liver VMs in cross sectional studies = prevalence
Liver VMs in HHT: what about natural history?
16 years of surveillance data

154 HHT pts with liver VMs, 198 controls (HHT without liver VMs)

Mean follow-up 44 months (range 12-181), 731 person-years for patients
Mean follow-up 42 months (range 11-179), 836 person-years for controls

39/154 (25%) patients had complications during follow up
Liver VMs in HHT: diagnosis  clinical features  outcome  management

Outcome predictors:

- stage 4 liver VMs
- genotype HHT2 (ALK1)
when liver VMs require treatment?

when symptomatic

first line treatment depends on the type of complication

Consensus Recommendations, Liver Int, 2006
AASLD, Vascular disorders of the liver, Hepatology 2009
International HHT Guidelines, J Med Genet 2011
AISF Guidelines, Vascular disorders of the liver, 2011
EASL Guidelines, Vascular diseases of the liver, 2016
Treatment

- **HOCF**: salt restriction, diuretics, beta-blockers, digoxins, angiotensin converting enzyme inhibitors, antiarrhythmic agents, cardioversions, and radiofrequency catheter ablation

- **Complications of portal hypertension**: as recommended in cirrhotic

- **Cholangitis**: antibiotics

**key issues:**
- Intensive approach
- Anemia correction!
Liver VMs in HHT: diagnosis clinical features outcome management

Table 3  Analysis of clinical events by liver vascular malformations (VM) stage

<table>
<thead>
<tr>
<th>Liver VMs stage</th>
<th>HOCF</th>
<th>Atrial fibrillation</th>
<th>Supraventricular tachycardia</th>
<th>Portal hypertension + ascites</th>
<th>Portal hypertension + GI bleeding</th>
<th>Encephalopathy</th>
<th>GI bleeding</th>
<th>Abdominal angina</th>
<th>Total</th>
</tr>
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<tbody>
<tr>
<td>0+</td>
<td>0</td>
<td>0</td>
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<td>5</td>
<td>7</td>
<td>1</td>
<td>0</td>
<td>1</td>
<td>35</td>
</tr>
<tr>
<td>Total</td>
<td>14</td>
<td>12</td>
<td>4</td>
<td>7</td>
<td>9</td>
<td>2</td>
<td>6</td>
<td>1</td>
<td>55</td>
</tr>
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</table>

HOCF high-output cardiac failure

a  At baseline

• outcome of treatments in 55 complications observed in 39 patients:

  complete response in 35 (63.7%)
  partial response in 12 (21.8%)
  no response (with progression to death) in eight (14.5%)

Buscarini E et al, DDS 2011
Consider invasive therapies for liver involvement by HHT only for otherwise intractable complications

What kind of invasive tx?
Transarterial embolization of liver VMs: palliative, temporizing, high-risk (only in patients who are not candidates for liver transplantation?)

Liver transplantation for ischemic biliary necrosis, for intractable high-output cardiac failure or complicated portal hypertension

MELD (Italian Transplant RB): 22 for intractable HOCF/PH, 40 for ischemic biliary necrosis

Consensus Recommendations, Liver Int, 2006
International HHT Guidelines, J Med Genet 2011
AISF Guidelines, Vascular disorders of the liver, 2011
EASL Guidelines, Vascular diseases of the liver, 2016
May 2007

F, 43 yo
Dyspnea, NYHA class III,
Limb edema, ascites
Atrial fibrillation (4 months)

Recurrent nosebleeds
Mucocutaneous telangiectases
Family history of nosebleeds

Liver VMs grade 4
PAPs 55 mmHg, CO 7 L/min
Intensive cardiological Tx: failure

HHT with high output cardiac failure, secondary to liver VMs grade 4: OLT 11/2008 alive and well, 12-2016
<table>
<thead>
<tr>
<th>OLT for liver VMs in HHT</th>
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<tbody>
<tr>
<td>number</td>
<td>67</td>
</tr>
<tr>
<td>sex</td>
<td>57 F (85%)</td>
</tr>
<tr>
<td>age</td>
<td>50.8 (27-71)</td>
</tr>
<tr>
<td>indication</td>
<td>HO CF 33 (49%)</td>
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<tr>
<td></td>
<td>cPH 5 (7%)</td>
</tr>
<tr>
<td></td>
<td>ISCHEMIC CHOL 15 (22%)</td>
</tr>
<tr>
<td></td>
<td>Mixed (HO CF/PH/ISCH CHOL) 14 (22%)</td>
</tr>
<tr>
<td>outcome</td>
<td>8 perioperative deaths (11%)</td>
</tr>
<tr>
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<td>5 year survival rate: 82-100%</td>
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<td>Cardiac: norm hemodynamic/clinical</td>
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<td>Nose/GI bleeding: markedly decreased</td>
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<tr>
<td></td>
<td>Improved QOL</td>
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</tbody>
</table>

Dupuis Girod S, Liver Transpl 2010
Nunez Viejo MA, Med Clin 2010
Cag M, Hepatol Int 2011
Maggi U, Transpl Proc 2013
Maestraggi Q, Medicine 2015

HOCF = High Output Cardiac Failure, PH = Portal Hypertension
Antiangiogenic drugs: is there a role for treatment of liver VMs in HHT?
<table>
<thead>
<tr>
<th>diagnosis</th>
<th>clinical features</th>
<th>outcome</th>
<th>management</th>
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<tbody>
<tr>
<td>BEVACIZUMAB for liver VMs in HHT</td>
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<tr>
<td>number</td>
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<td>34</td>
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</tr>
<tr>
<td>sex</td>
<td></td>
<td>33 F</td>
<td></td>
</tr>
<tr>
<td>age</td>
<td></td>
<td>56 (25-68)</td>
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</tr>
<tr>
<td>indication</td>
<td></td>
<td>HCO 27</td>
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<td></td>
<td></td>
<td>HOCF 1</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td>ISCHEMIC CHOL 5</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>MIXED HOCF/PH 1</td>
<td></td>
</tr>
<tr>
<td>outcome</td>
<td></td>
<td>complete response 11 (32%)</td>
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<td></td>
<td></td>
<td>partial response 18 (53%)</td>
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<tr>
<td></td>
<td></td>
<td>no response 5 (15%)</td>
<td></td>
</tr>
<tr>
<td>adverse events</td>
<td></td>
<td>93 - 3 grade 4 AE</td>
<td></td>
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<tr>
<td>recurrence after drug withdrawal</td>
<td></td>
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</tr>
</tbody>
</table>

HOCF = High output cardiac failure, PH = Portal Hypertension  
HCO = high cardiac output

Mitchell A, Liver Transplant 2008  
Dupuis Girod S, JAMA 2012  
Chavan A, Vasa 2013  
Faughnan M, J Hepatol 2013  
Maestraggi Q, Medicine 2015  
Stickel F, Liver Intern 2017
Liver VMs in HHT: conclusions

who: woman, in her fifties, HHT2

incidence of liver VM complications: 25% of pts with liver VMs will show symptoms over follow-up, with a 3.6 and 1.1%/year of morbidity/mortality for liver VMs

how liver VMs get complicated: As it was thought, HOCF represents the predominant complication associated with liver VMs in HHT. Differently from what was thought: Complicated portal hypertension occurs at a rate comparable to that of HOCF
Surveillance: liver VMs grade 4!

High response rates to treatments for liver VM complications: caution when considering major treatment methods (embo, OLT; bevacizumab?)

Bevacizumab: an option for patients not amenable to OLT either over 65 years or poor candidates for surgery (?)

If these latter respond to the drug: OLT with a “fast-track” (?)

take advice from a medical team with expertise in HHT before making any decision regarding treatment of liver VMs, and notably OLT