Acquired Von Willebrand Syndrome and Heyde’s Syndrome

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Objectives

• Describe acquired von Willebrand syndrome (AVWS) clinical presentation and diagnosis
• Describe the association of acquired von Willebrand syndrome with aortic stenosis and Heyde’s syndrome
• Describe laboratory and clinical characteristics of aortic stenosis patients with AVWS
• Discuss treatment options for acquired von Willebrand syndrome in aortic stenosis
Acquired Von Willebrand Syndrome

• Acquired defect in von Willebrand factor
  – Quantitative or qualitative
• Generally manifests as mucocutaneous bleeding in patients without personal or family history of bleeding disorder
• Seen in association with multiple categories of diseases
Acquired Von Willebrand Syndrome

- Seen in association with multiple categories of diseases
  - Lymphoproliferative disorders (MGUS)
  - Myeloproliferative disorders (CML)
  - Solid tumors (Wilm’s tumor)
  - Autoimmune/endocrine (Hypothyroidism)
  - Cardiovascular (Aortic stenosis)
  - Medications (Valproic acid)
  - Other (Gastrointestinal angiodysplasia)
Mechanisms of VWF defect in AWVS

• Heterogeneous
  – Decreased biosynthesis of VWF in hypothyroidism
  – Accelerated removal of VWF from the plasma in most other associated conditions
    • Autoantibodies against VWF
      ➔ Clearance of immune complexes
    • Adsorption of VWF to malignant cells
      ➔ Clearance
  • Proteolysis of VWF multimers under conditions of high shear stress
Diagnosis of AVWS

• Bleeding pattern
  – Typically presents with mild to moderately severe mucocutaneous bleeding pattern similar to congenital VWD
• Demonstration of a plasma VWF abnormality
  – Usually a decrease in VWF:Ag and FVIII activity
  – Decrease in VWF:RCo or VWF:CB
  – Usually a Type 2 pattern
    • Decrease in VWF:RCo/VWF:Ag or VWF:CB/VWF:Ag ratios
    • Abnormal multimer electrophoresis
      – Decreased levels of high molecular weight multimers
• Identification of a causal underlying condition
Aortic stenosis, GI Bleeding, and AVWS

- Dr. Edward Heyde reported his observation of 10 cases of aortic stenosis with severe gastrointestinal bleeding without known cause in 1958 NEJM
- Greenstein et al, 1986: Identified submucosal angiodysplasia as the source GI bleeding in patients with aortic stenosis
- Two groups in 1986: Reported loss of high-molecular-weight multimers of VWF in patients with aortic stenosis
- King et al, 1987: Reported cessation of bleeding in 14 patients with aortic stenosis after valve replacement
- Warkentin et al, 1992, Lancet:
  - Hypothesized they Heyde’s syndrome is a form of type IIA AVWS
  - Proposed mechanism of activation of VWF is flow through high shear stenotic valve and subsequent clearance from circulation
- Heyde’s syndrome:
  - Syndrome of gastrointestinal bleeding from angiodysplasia in the presence of aortic stenosis due to AVWS-IIA
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Proteolytic Cleavage of VWF in Aortic Stenosis

VWF and Angiogenesis

• VWF may play a role in negative regulation of angiogenesis
  – Cell culture data show that lack of VWF in the Weibel-Palade bodies of endothelial cells triggers angiogenesis
  – VWF-deficient mice demonstrated increased angiogenesis and a larger vascular network

• Angiogenesis in AVWS may contribute to angiodysplasia
Acquired von Willebrand Syndrome in Aortic Stenosis

André Vincentelli, M.D., Sophie Susen, M.D., Thierry Le Tourneau, M.D., Ph.D., Isabelle Six, Ph.D., Olivier Fabre, M.D., Francis Juthier, Anne Bauters, Christophe Decoene, M.D., Jenny Goudemand, M.D., Ph.D., Alain Prat, M.D., and Brigitte Jude, M.D., Ph.D.

- Study of aortic stenosis patients before and after valve replacement surgery
- Describes laboratory and clinical characteristics over time

Vincentelli et al. NEJM 2003: 349; 343-349.
Patient Population

• Prospective study enrolled 50 consecutive patients referred for aortic stenosis

• Patient population:
  – 42 had severe AS (mean gradient of >50 mm Hg or indexed effective orifice area of <0.5 cm²/m² of BSA)
    • Underwent aortic valve replacement
  – 8 had only moderate AS
    • Did not undergo surgery
Bleeding in Patients with Severe Aortic Stenosis Prior to Surgery

- During the six months before surgery, 11/42 patients with severe AS had episodes of bleeding in the six months before surgery (2 on anticoagulants)

<table>
<thead>
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<th>No. of Events</th>
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<tbody>
<tr>
<td>Spontaneous bleeding</td>
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<td>Epistaxis</td>
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<tr>
<td>Ecchymosis</td>
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<tr>
<td>Gastrointestinal hemorrhage</td>
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<tr>
<td>Hematuria</td>
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<tr>
<td>Gingivorrhagia</td>
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<tr>
<td>Induced bleeding</td>
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<tr>
<td>Dental extraction</td>
<td>2</td>
</tr>
</tbody>
</table>
Laboratory Measurements

- **PFA closure time (Collagen/ADP)**
  - Prolonged in 92% of patients with severe AS (mean 0.64 s)
  - Prolonged in 50% of patients with moderate AS (mean 0.80 s)

- **VWF:CB**
  - Decreased in 67% of patients with severe AS
  - Decreased in 25% of patients with moderate AS

- **Percentage of highest-molecular-weight multimers**
  - Decreased in 79% of patients with severe aortic stenosis
  - Decreased in 75% of patients with moderate AS
Correlation of Severity of Stenosis with VWF Abnormality

**Figure 1.** Relation between Von Willebrand Factor Abnormalities and Severity of Stenosis, Represented as the Mean Transvalvular Gradient Plotted against the Percentage of Highest-Molecular-Weight Von Willebrand Factor Multimers ($r = -0.56, P < 0.001$). The line is the regression line.
Immediate Post-op Correction of Lab Abnormalities

- Percentage of highest-molecular-weight multimers and PFA values corrected in all patients on days 1 and 7
Bleeding Status 6 Months Post-surgery

• One patient presented with early homograft valve stenosis
  – Repeated epistaxis was observed at the onset of restenosis
• Other patients were asymptomatic at 6 months, without bleeding episodes, even those with mechanical prosthesis requiring oral anticoagulant therapy
Patient-Prosthesis Mismatch

• Patient-prosthesis mismatch:
  • Effective orifice area of the inserted prosthetic valve is too small in relation to body size
  • Generates higher than expected transvalvular pressure gradients
  • Tissue ingrowth and endothelialization further reduces the effective orifice area after insertion
• Mismatch between patient and prosthesis was observed in 10 cases

6-month Follow-up Levels of Highest Molecular Weight VWF Multimers

**Figure 3.** Mean (±SE) Evolution of Highest-Molecular-Weight Von Willebrand Factor Multimers after Valvular Replacement in Patients with and Patients without a Mismatch between Patient and Prosthesis.
Study Conclusions

• High frequency of AVWS in severe aortic stenosis
• Correlation of severity of VWF abnormalities with degree of stenosis
  – Suggests proteolysis of high molecular weight multimers is the major mechanism of AVWS is AS
• Valve replacement is corrective
Treatment options for AVWS in Aortic Stenosis

• For AVWS with AS, corrective surgery should be undertaken as soon as possible
  – Pre- and intra-operative VWF replacement?

• Additional treatment options (variably effective and data is limited):
  – VWF-containing concentrate
  – Antifibrinolytic
  – Estrogen therapy
  – Octreotide

  • Mechanisms may include decreased splanchnic blood flow, increased vascular resistance, improved platelet aggregation
References

- Tiede et al. Blood 2011: 117; 6777-6785
- Franchini M and Mannucci P. British Journal of Haematology 2013: 161; 177-182.
- Figuinha et al. Arq Bras Cardiol 2011: 96; e42-e45.
- Vincentelli et al. NEJM 2003: 349; 343-349.
Thank you