Hemoglobinopathies (& Hereditary Hemolytic Anemias): A New Hypercoagulable State?

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Case presentation: A Splitting Headache

• 42 y.o. male presents with an acute-onset severe frontal headache while sitting on his front porch

• Past Medical History:
  ▫ Sickle cell trait
  ▫ Splenectomy for painful splenomegaly at age 32
  ▫ Pulmonary embolism at ages 33 and 36, idiopathic, treated with 1 year anticoagulation each

• Meds: None

• Family history: Father with sickle cell trait, brother with MS, mother healthy.
A Splitting Headache (cont)

• Labs: WBC 8.7, Hgb 12.2, Hct 37.1, MCV 73.8, platelets 241

• Admission MRI/A head: Sagittal vein thrombosis and bilateral transverse sinus thrombosis with associated frontal and cerebellar venous infarcts.

• Hypercoagulable work-up: Factor V Leiden, prothrombin 20210 mutation, protein C, protein S, dRVVT, antiphospholipid Abs negative.

• Hemoglobin variant: Hgb A 22.2%, Hgb S 68.3%, Hgb F 3.1%
Oh, no! Wait. Let’s backtrack: A hypothetical conversation with the patient

- You sure you’ve never been told you have sickle cell disease? Yes, I’m sure.

- You sure you don’t have any siblings with the disease? Yes, I’m sure.

- Is your mother anemic or maybe microcytic? Uh, what? I don’t know.

- You sure you’ve never had a pain crisis, pneumonia, eye problems, hip pain, anything? Now that you mention it, something changed after my splenectomy, I developed a pretty bad pneumonia immediately after the surgery, and now all these clots...
This begs the questions ...

- Are hemoglobinopathies (and hereditary hemolytic anemias) risk factors for venous thromboembolism?

- Is this a typical story for VTE in a sickle cell patient?

- What’s splenectomy got to do with it?
Thrombosis and hemolytic anemias: It’s all in the blood

Virchow’s Triad

- **Endothelial damage**: Direct vascular damage from ischemic injury and free hemoglobin

- **Stasis**: Decreased blood flow secondary to erythrocyte adhesion and increased viscosity, especially in low flow, hypoxic environments (arterioles, venous beds)

- **Hypercoagulability**: Externalization of phosphatidylserine (PS) on RBCs leads to subsequent thrombin generation, platelet adhesion, and WBC activation (and many, many other factors)

The majority of research, however, has focused on *microvascular arterial* complications of hemolytic anemias and hemoglobinopathies such as stroke, osteonecrosis, and pulmonary hypertension.

So, is the venous system even affected? Let’s see the data.
What we know about VTE in Sickle Cell Disease (embarrassingly little)

- **Observation #1:** Based on a large de-identified database of 1.8 million (say what?) SCD patients hospitalized from 1979-2003, the prevalence of PE (but NOT DVT) was higher in SCD patients <40 years of age compared to African-American controls.

- This has led to assumptions that PE represents *in situ* pulmonary thrombosis rather than embolic phenomenon in SCD patients.
- However, de-identified data may have led to an underestimation of true prevalence since SCD patients have high hospitalization rates.
What we know about VTE in Sickle Cell Disease (embarrassingly little)

- **Observation #2:** Pulmonary embolism (PE) is common in autopsy studies of patients with SCD (25-50%), even in studies that differentiate between microvascular thrombi and macrovascular embolism.

**Autopsy study of unexpected deaths from 1990-2004 at Emory**

*The most common pulmonary findings at autopsy of sickle cell patients (n=21)*

**FIGURE 6.** Pulmonary edema was seen in almost half of the cases (47.6%), and thromboembolism was observed in 38% of cases. Significant proportion of sickle cell patients showed different stages of pulmonary hypertension (33.3%) and fat embolism (33.3%).
In a “Sea of Blood”:
What we know about VTE in the Thalassemias

• **Observation #1:** Venous thrombosis is common in patients with β-thalassemia intermedia (β-TI)
  ▫ Prevalence estimates for VTE in β-TI patients range from 4-29%, depending on the age of the cohort

• **Observation #2:** But VTE is uncommon in β-thalassemia major (β-TM) patients
  ▫ Prevalence estimates for VTE in β-TM patients range from 1-2%

Thrombotic events in a cohort of 6,672 β-TM & 2,188 β-TI patients

In a “Sea of Blood”:
What we know about VTE in the Thalassemias

• **Observation #3:** VTE is observed in a variety of forms in β-thalassemia patients. (Not just PE)

Thrombotic events in a cohort of 6,672 β-TM & 2,188 β-TI patients

In a “Sea of Blood”:
What we know about VTE in the Thalassemias

• **Observation #4:** Splenectomy significantly increases the risk of thrombosis in patients with β-TI.
  - 94-96% of β-TI patients with VTE have undergone splenectomy.
  - 24% of β-TI patients who underwent splenectomy subsequently developed thrombosis, with median time from splenectomy to thrombosis of 8 years.

Hemoglobinopathy and thrombosis: The Hopkins Experience

• Retrospective cohort study of all patients evaluated in the Sickle Cell Center for Adults at Hopkins from 8/2008 to 1/2012

• Patient characteristics
  ▫ 279 patients with SS/Sβ⁰ genotype or sickle cell anemia (SCA)
  ▫ 84 patients with SC disease
  ▫ 39 patients with Sβ⁺ thalassemia
  ▫ 2 patients with other sickle variants

  ▫ 257 patients age < 40 years
  ▫ 147 patients age > 40 years
  ▫ Median age of cohort = 35.8 years (19-81 years old)
The Hopkins Experience: We tell it like it is

All SCD Patients (n = 404)

- Non-catheter-related VTE: 25%
- Catheter-related VTE: 19%
- No VTE: 6%
The Hopkins Experience: We tell it like it is

VTE type (n = 101)

- 44% DVT only
- 24% DVT + PE
- 29% PE only
- 3% Other
## Prevalence of VTE, by genotype

<table>
<thead>
<tr>
<th>Variable</th>
<th>All SCD</th>
<th>SCA (SS/Sβ⁰)</th>
<th>Sickle Variants</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total patients</td>
<td>404</td>
<td>279</td>
<td>125</td>
<td></td>
</tr>
<tr>
<td>Any VTE</td>
<td>101 (25%)</td>
<td>63 (23%)</td>
<td>38 (30%)</td>
<td>0.093</td>
</tr>
<tr>
<td>Deep venous thrombosis</td>
<td>74 (18%)</td>
<td>51 (18%)</td>
<td>23 (18%)</td>
<td>0.977</td>
</tr>
<tr>
<td>Pulmonary embolism</td>
<td>53 (13%)</td>
<td>29 (10%)</td>
<td>24 (19%)</td>
<td>0.015</td>
</tr>
<tr>
<td>Other VTE</td>
<td>4 (1%)</td>
<td>2 (1%)</td>
<td>2 (2%)</td>
<td>0.055</td>
</tr>
<tr>
<td>Non-catheter-related VTE</td>
<td>76 (19%)</td>
<td>43 (15%)</td>
<td>33 (26%)</td>
<td>0.009</td>
</tr>
</tbody>
</table>
### VTE characteristics, by genotype

<table>
<thead>
<tr>
<th>Variable</th>
<th>All SCD</th>
<th>SCA (SS/Sβ0)</th>
<th>Sickle Variants</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Median age at 1st VTE (yrs)</strong></td>
<td>29.9</td>
<td>28.0</td>
<td>34.2</td>
<td>0.006</td>
</tr>
<tr>
<td>Total VTE</td>
<td>101</td>
<td>63</td>
<td>38</td>
<td></td>
</tr>
<tr>
<td>Catheter-related VTE</td>
<td>25 (25%)</td>
<td>20</td>
<td>5</td>
<td>0.036</td>
</tr>
<tr>
<td>Non-catheter-related VTE</td>
<td>76 (75%)</td>
<td>43</td>
<td>33</td>
<td></td>
</tr>
<tr>
<td>VTE recurrence</td>
<td>25 (25%)</td>
<td>19</td>
<td>6</td>
<td>0.071</td>
</tr>
<tr>
<td>Median time to recurrence (yrs)</td>
<td>1.8</td>
<td>3.1</td>
<td>6.6</td>
<td>0.062</td>
</tr>
</tbody>
</table>
## Associated Factors for Non-catheter-related VTE in SCD patients

<table>
<thead>
<tr>
<th>Variable</th>
<th>No VTE (n = 303)</th>
<th>Non-CVC VTE (n = 76)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Demographics</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age* (years)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>18-30</td>
<td>117 (38.6)</td>
<td>21 (27.6)</td>
<td>0.144</td>
</tr>
<tr>
<td>31-40</td>
<td>84 (27.7)</td>
<td>21 (27.6)</td>
<td></td>
</tr>
<tr>
<td>41-50</td>
<td>68 (22.4)</td>
<td>19 (25.0)</td>
<td></td>
</tr>
<tr>
<td>51-60</td>
<td>20 (6.6)</td>
<td>11 (14.5)</td>
<td></td>
</tr>
<tr>
<td>&gt;60</td>
<td>14 (4.6)</td>
<td>4 (5.3)</td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>171 (56.4)</td>
<td>52 (68.4)</td>
<td>0.058</td>
</tr>
<tr>
<td>Sickle cell variant genotype</td>
<td>87 (28.7)</td>
<td>33 (43.4)</td>
<td><strong>0.014</strong></td>
</tr>
<tr>
<td><strong>Co-morbidities</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>End-stage renal disease</td>
<td>7 (2.3)</td>
<td>3 (3.9)</td>
<td>0.426</td>
</tr>
<tr>
<td>Avascular necrosis</td>
<td>103 (34.0)</td>
<td>35 (46.1)</td>
<td>0.051</td>
</tr>
<tr>
<td>Stroke</td>
<td>37 (12.2)</td>
<td>10 (13.2)</td>
<td>0.823</td>
</tr>
<tr>
<td>Leg Ulcer</td>
<td>28 (9.2)</td>
<td>9 (11.8)</td>
<td>0.495</td>
</tr>
<tr>
<td>TRV ≥ 2.5 m/s</td>
<td>93 (30.7)</td>
<td>34 (44.7)</td>
<td><strong>0.020</strong></td>
</tr>
</tbody>
</table>
# Risk factors for non-catheter VTE, Multivariate model

<table>
<thead>
<tr>
<th>Variable</th>
<th>RR</th>
<th>CI</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age</strong> (years)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>31-40</td>
<td>1.26</td>
<td>0.74-2.13</td>
</tr>
<tr>
<td>41-50</td>
<td>1.27</td>
<td>0.74-2.19</td>
</tr>
<tr>
<td>51-60</td>
<td>1.85</td>
<td>0.98-3.51</td>
</tr>
<tr>
<td>&gt; 60</td>
<td>0.87</td>
<td>0.32-2.41</td>
</tr>
<tr>
<td><strong>Female</strong></td>
<td>1.52</td>
<td>1.00-2.34</td>
</tr>
<tr>
<td><strong>Sickle variant genotype</strong></td>
<td>1.77‡</td>
<td>1.18-2.66</td>
</tr>
<tr>
<td><strong>Avascular necrosis</strong></td>
<td>1.46</td>
<td>0.98-2.17</td>
</tr>
<tr>
<td><strong>TRV ≥ 2.5 m/s</strong></td>
<td>1.65†</td>
<td>1.12-2.45</td>
</tr>
</tbody>
</table>

† p<0.05, ‡ p<0.01
Is there a pattern?

Arterial events = β-TM
Venous events = β-TI

Arterial events = SCA
Venous events = Sickle variant genotypes

Viscosity/High hemoglobin
Vaso-occlusion

Pulmonary hypertension
Leg ulcers
Childhood stroke
Venous thromboembolism

Retinopathy
Osteonecrosis

Hemolysis/Low hemoglobin
Endothelial dysfunction

Let’s crunch the numbers: VTE in SC and Sβ+ thalassemia

<table>
<thead>
<tr>
<th>Variable</th>
<th>No VTE (n = 69)</th>
<th>VTE (n = 26)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>42</td>
<td>47</td>
<td>0.043*</td>
</tr>
<tr>
<td>WBC (K/cu mm)</td>
<td>8.1</td>
<td>8.3</td>
<td>0.665</td>
</tr>
<tr>
<td>Hemoglobin (g/dL)</td>
<td>10.8</td>
<td>11.6</td>
<td>&lt;0.001*</td>
</tr>
<tr>
<td>Platelet count (K/cu mm)</td>
<td>291</td>
<td>317</td>
<td>0.401</td>
</tr>
<tr>
<td>Reticulocyte count</td>
<td>3.8%</td>
<td>3.4%</td>
<td>0.415</td>
</tr>
<tr>
<td>Absolute retic (K/cu mm)</td>
<td>149</td>
<td>143</td>
<td>0.724</td>
</tr>
<tr>
<td>History of splenectomy</td>
<td>4 (5.8%)</td>
<td>7 (27%)</td>
<td>0.004*</td>
</tr>
</tbody>
</table>

* Significant on both bivariate & multivariate analysis
Is SCD the new PV?

Viscosity in Normal AA blood

Viscosity in Deoxygenated SS blood

Blood viscosity-shear rate relations for deoxygenated 100 percent SS RBCs suspended in autologous plasma at 0.20 (□), 0.25 (○), 0.30 (●), and 0.40 Hct (●).

The hypercoagulability of asplenia in hereditary hemolytic anemias

**Hereditary spherocytosis**

443 patients from families of hereditary spherocytosis (290 affected, 153 unaffected), followed from 1960-2003.

Estimated cumulative incidence by age 70 of venous events:
- ~20% for splenectomized affected pts
- ~5% for unaffected individuals or those without splenectomy
- No difference in rates between unaffected & non-splenectomized pts

**Unstable hemoglobins**

Systematic review of 304 reports of patients with unstable hemoglobins

Thrombotic events – 82 cases (27%)
- Age at thrombosis 20-35
- VTE type = PE, DVT, Pulm htn (leg ulcers, priapism also seen)
- 84% of clots occurred in splenectomized pts
- Of the reported patients with splenectomy, 62% had a history of clot.


Courtesy of Dr. Kickler
But why?

• Unclear mechanism
• Multiple theories:
  • Increase in circulating abnormal cells with PS exposure → increased thrombin generation
  • Increase in intravascular hemolysis
  • Increased hemoglobin +/- platelet counts
In sickle cell patients, is functional asplenia the same as no spleen?

Pitted RBCs

- RBC pitting is used as a surrogate to estimate splenic function in patients with SCD.

- Pit count thresholds for functional asplenia have been shown to correlate to risk of infectious complications in SCD.

- In pts with SC, for example, pit count of 20% correlates with absent splenic uptake on spleen scans; however, pit counts are 2 fold higher in patients s/p surgical splenectomy.

- Degree of splenic dysfunction may matter with thrombotic risk – may explain why surgical splenectomy appears to be a risk factor for VTE in sickle patients.

Why this really matters: Mortality related to VTE in SCD

Mortality by Non-Catheter-VTE status

Proportion Surviving

Age

NCVTE = 0

NCVTE = 1

p = 0.001
### Why this really matters: Risk factor model for mortality in SCD

<table>
<thead>
<tr>
<th>Variable</th>
<th>RR</th>
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</thead>
<tbody>
<tr>
<td><em><em>Age</em> (years)</em>*</td>
<td></td>
<td></td>
</tr>
<tr>
<td>31-40</td>
<td>1.08</td>
<td>0.42-2.77</td>
</tr>
<tr>
<td>41-50</td>
<td>1.55</td>
<td>0.65-3.69</td>
</tr>
<tr>
<td>51-60</td>
<td>0.52</td>
<td>0.06-4.77</td>
</tr>
<tr>
<td>&gt; 60</td>
<td>1.03</td>
<td>0.16-6.55</td>
</tr>
<tr>
<td><strong>Female</strong></td>
<td>0.56</td>
<td>0.27-1.18</td>
</tr>
<tr>
<td><strong>Non-SCA</strong></td>
<td>0.57</td>
<td>0.21-1.58</td>
</tr>
<tr>
<td><strong>Non-CVC VTE</strong></td>
<td>3.63†</td>
<td>1.66-7.92</td>
</tr>
<tr>
<td><strong>End-stage renal disease</strong></td>
<td>3.03†</td>
<td>1.16-7.93</td>
</tr>
<tr>
<td><strong>Avascular necrosis</strong></td>
<td>0.58</td>
<td>0.26-1.28</td>
</tr>
<tr>
<td><strong>Stroke</strong></td>
<td>1.47</td>
<td>0.62-3.45</td>
</tr>
<tr>
<td><strong>Leg ulcer</strong></td>
<td>1.00</td>
<td>0.29-3.49</td>
</tr>
<tr>
<td><strong>TRV ≥ 2.5 m/s</strong></td>
<td>3.40‡</td>
<td>1.47-7.87</td>
</tr>
</tbody>
</table>

† p<0.05, ‡ p<0.01
Conclusions

• Hemoglobinopathies & hemolytic anemias are hypercoagulable states and are associated with high rates of VTE.

• The prevalence & age at first VTE in all hemolytic syndromes is similar to that seen in patients with high-risk thrombophilias such as protein C/S & ATIII deficiency.

• Modifying factors for risk of VTE in hemoglobinopathies and hemolytic anemias appear to be: age, genetic variant, baseline hemoglobin/viscosity, degree of splenic dysfunction, etc.

• VTE is an independent risk factor for death in SCD patients.

• Potential role for prophylactic anticoagulation in:
  ▫ High risk patients (if they can be identified)
  ▫ Patients with hemolytic anemias (namely SCD) & pulmonary htn as there may be a pathogenic link between VTE and in situ thrombosis seen in patients with hemolysis-associated pulm htn.