Is C2 Disease Progressive?

Mark H. Meissner, MD

I Have No Disclosures Relevant To This Presentation

What is C2 Progression?

The Edinburgh Vein Study – Lee AJ, JVS Ven & Lymph 2015

- Progression within C2 category
  - Worsened unilateral severity
  - Progression to bilateral disease

C2 Progression

The Edinburgh Vein Study – Lee AJ, JVS Ven & Lymph 2015

- 13.4 yr follow-up of general population sample (n = 880)
- Progression of C2 to C3 – C6 (n = 86)
  - C3 – 67 (24.8%, 1.8% per year)
  - C4 – 19 (7%, 0.5% per year)
  - C5, 6 - 0

Family hx - Dominant risk factor for progression to CVI (OR 1.85, 1.10 – 3.22)

The Progression of 1° CVD

The Bonn Vein Study, Rabe E, in press

- 6.6 year follow-up of Bonn I participants
- 2% per year progression to CVI (C3 – C6)
- Risk factors for progression
  - Age
  - Arterial Hypertension
  - Obesity

<table>
<thead>
<tr>
<th>C2</th>
<th>C3</th>
<th>C4a</th>
<th>C4b</th>
<th>C5</th>
<th>C6</th>
<th>Any</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n (%)</td>
<td>n (%)</td>
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<tr>
<td>C0 + C1 (1269)</td>
<td>161 (12.7)</td>
<td>95 (7.5)</td>
<td>22 (1.7)</td>
<td>1 (0.1)</td>
<td>3 (0.2)</td>
<td>0</td>
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<tr>
<td>C2 (91) non saph</td>
<td>15 (16.5)</td>
<td>2 (2.2)</td>
<td>1 (1.1)</td>
<td>0</td>
<td>0</td>
<td>19.8</td>
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<tr>
<td>C2 (132) saphenous</td>
<td>28 (21.2)</td>
<td>14 (10.6)</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>31.8</td>
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</table>
| C3 (120) | 9 (7.5) | 0 | 0 | 0 | 6.4%
| C3 (27) | 1 (3.8) | 1 (3.8) | 6.7%
| C5 (15) | 0 | 0 | 8%
CVD Progression
Pacific Vascular Symposium 6, J Vasc Surg 2010

- C2 disease will worsen in 40% of patients over 10 – 15 yrs

But…
- Most patients with CVD do not progress to C4 – 6
- Advanced CVD is a multifactorial disease
  - Family history
  - Previous DVT
  - Age
  - Obesity
- Number needed to prevent 1 ulcer (NNT) is low and will likely remain unknown

Genetic Susceptibility to CVD
Ellinghaus E, Nature 2017

- Genome-wide genotyping with SNP arrays
  - Discovery panel (323 C2 – C4 patients, 4619 controls)
  - Replication panels (1946 patients, 3146 controls)
- Three CVD susceptibility loci
  - EFEMP1 – matrix glycoprotein fibulin-3
  - KCNHS – potassium voltage-gated channels
  - SKAP2 – leukocyte adhesion
- Responsible for 2% of variance in heritability

Genetic Factors in CVD Progression
Gemmati, J Vasc Surg 2009

- Multiple postulated single nucleotide polymorphisms (SNPs)
  - Iron metabolism
    - HFE (hemochromatosis protein)
    - Ferroportin gene (FPN)
  - Wound healing (MMP12)
  - Coagulation (Factor XIII, protective)
  - DNA array genotyping in 638 subjects
    - 333 C3 – C6 patients
    - 305 healthy controls

<table>
<thead>
<tr>
<th>Gene</th>
<th>SNP</th>
<th>VLU Risk</th>
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<tbody>
<tr>
<td>HFE</td>
<td>C282Y</td>
<td>6 – 7X</td>
</tr>
<tr>
<td>FPN</td>
<td>8GG</td>
<td>5X</td>
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<tr>
<td>MMP12</td>
<td>82AA</td>
<td>2X</td>
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</table>

Demographic & Environmental Factors
Age
Gender
Obesity

Genetic Factors
HFE
FPN
Factor XIII
Unidentified Factor

Conclusions

- Disease progression is a multifactorial process
  - Venous disease may be the promoting factor
  - Other deterministic factors
    - Environmental & demographic factors
    - Genetic factors
- Attributing progression to venous disease alone is overly simplistic
- The value of prophylactic intervention for unselected C2 – 3 disease is unlikely to be demonstrated
- Factors determining progression to C4 – 6 disease need to be better elucidated