Is C2 Disease Progressive?

Mark H. Meissner, MD
Peter Gloviczki Professor of Venous & Lymphatic Disorders
University of Washington School of Medicine
Seattle, WA

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
Pittaluga P, Phlebology 2008

- U/S characterization of 2275 C0 – C6 limbs
- 5 patterns of reflux

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
- 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 1º CVD
The Bonn Vein Study II, 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

C2
C3
C4
C5
C6
Any

<table>
<thead>
<tr>
<th></th>
<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>n</td>
<td>n (%)</td>
<td>n</td>
<td>n (%)</td>
<td>n (%)</td>
<td>n</td>
<td>n (%)</td>
<td>n (%)</td>
</tr>
</tbody>
</table>
| C0=C1 (1269) | 161 (12.7) | 95 (7.5) | 22 (1.7) | 1 (0.1) | 3 (0.2) | 0 | 22.2 %
| C2 (91) non saph | 15 (16.5) | 2 (2.2) | 1 (1.1) | 0 | 0 | 19.8 %
| C2 (132) saphenous | 28 (21.2) | 14 (10.6) | 0 | 0 | 31.8 %
| C3 (64) | 9 (6.4) | 0 | 0 | 0 | 6.4 %
| C4 (25) | 1 (4.0) | 1 (4.0) | 6.7 %
| C5 (5) | 0 | 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

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

Genetic Factors

- HFE
- FPN
- Factor XIII
- Unidentified Factors

Demographic & Environmental Factors
- Age
- Gender
- Obesity

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