Positive Family History of Aortic Dissection Dramatically Increases Dissection Risk in Family Members

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Presented at the 5th International Meeting on Aortic Diseases
Liège, Belgium

September 16th, 2016
Clinical Scenario

A 45-year-old man comes for consultation
• Asymptomatic
• An enlarged ascending aorta: 4.5 cm
• His father had an aortic dissection 20 years ago

What is his risk of developing aortic dissection?
• Is it higher.
• But how much higher?
• What would you suggest? Surgical repair or wait?
Objectives

To examine the impact of a positive family history of aortic dissection (FHAD) on the risk of developing aortic dissection (AD) among 1st-degree family members, focusing on:

• age at which AD occurred

• years of exposure to FHAD in adulthood before AD occurred

• annual probability of developing a new AD per adult 1st-degree relative
Number of Events per Exposure Year in Adult First-Degree Relatives

\[
\text{No. of AoD events per exposure year in first degree relatives} = \frac{\text{Total No. of AoD events that occurred in the family}}{\sum [(\text{current age of relative or age at death or aortic surgery} - 18) + (\text{Patient age at AoD} - 18)]}
\]

Explanation

- Adulthood starts at the age of 18
- Total No. of AoD events = No. of AoDs occurred in 1st-degree relatives
- Exposure years for patient = Age at dissection - 18
- Exposure years for alive relative = Current age - 18
- Exposure years for dead relative = Age at death - 18
- Exposure years for relatives with aortic surgery = Age at surgery - 18
Exposure Years per Adult First-Degree Relative per Event

Exposure years per first degree relative per event

\[ \sum \left( \frac{\text{current age of relative or age at death or aortic surgery} - 18}{\text{total AoD events in the family}} + \left(\text{patient age at AoD} - 18\right) \right) \times \text{No. of first degree relatives} \]

Explanation

• Adulthood starts at the age of 18
• Total No. of AoD events = No. of AoDs occurred in 1st-degree relatives
• No. of 1st-degree relatives = 2 parents + No. of siblings & children + 1
• Exposure years for patient = Age at dissection - 18
• Exposure years for alive relative = Current age - 18
• Exposure years for dead relative = Age at death - 18
• Exposure years for relatives with aortic surgery = Age at surgery - 18
Incidence Rates and Odds Ratios in Siblings and Children-Parent Settings

Incidence rate of AoD in siblings = \( \frac{\text{No. of siblings in whom AoD occurred}}{\text{Total No. of siblings in this study}} \)

\[
\text{OR of AoD in siblings} = \frac{\frac{\text{No. of siblings in whom AoD occurred}}{\text{Total No. of siblings in this study}}}{1 - \frac{\text{No. of siblings in whom AoD occurred}}{\text{Total No. of siblings in this study}}}
\]

Rate of dissected children per parent = \( \frac{\text{No. of children in whom AoD occurred}}{\text{Total No. of parents in this study}} \)

\[
\text{OR of AoD in parent to children setting} = \frac{\frac{\text{No. of children in whom AoD occurred}}{\text{Total No. of parents in this study}}}{1 - \frac{\text{No. of children in whom AoD occurred}}{\text{Total No. of parents in this study}}}
\]
Flow Diagram of Pedigrees Created

 Patients with thoracic aortic disease at Yale  
  (n = 3263)

 Patients with AoD/IMH/PAU  
  (n = 460)

 Questionnaires sent  
  (n = 325)

  Expired patients  
  (n = 135)

 No response/undelivered  
  (n = 225)

 Questionnaire Returned  
  (n = 100)

 Patients with positive FHAD  
  (n = 32)

 Patients with negative FHAD  
  (n = 68)
## Risk of aortic dissection in patients with negative vs positive family history

<table>
<thead>
<tr>
<th>Variables</th>
<th>Patients with negative FHAD (n = 68)</th>
<th>Patients with Positive FHAD (n = 32)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age at dissection (year)</td>
<td>62.4 ± 13.0</td>
<td>54.7 ± 16.8</td>
<td>0.013</td>
</tr>
<tr>
<td>Type of dissection (Stanford A/B)</td>
<td>24/8</td>
<td>46/22</td>
<td>0.454</td>
</tr>
<tr>
<td>Mean number of 1st-degree relatives</td>
<td>7.3 ± 2.2</td>
<td>7.5 ± 3.2</td>
<td>0.751</td>
</tr>
<tr>
<td>Mean number of siblings</td>
<td>3.4 ± 2.0</td>
<td>3.4 ± 1.7</td>
<td>0.957</td>
</tr>
<tr>
<td>Mean number of AD events</td>
<td>1.0 ± 0.0</td>
<td>2.3 ± 0.6</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Total exposure years in adulthood</td>
<td>313.8 ± 108.5</td>
<td>322.7 ± 199.7</td>
<td>0.768</td>
</tr>
<tr>
<td>Number of ADs per year per adult relative (%)</td>
<td>0.359 ± 0.014</td>
<td>0.997 ± 0.057</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Exposure years per relative before AD</td>
<td>43.1 ± 8.5</td>
<td>18.3 ± 6.7</td>
<td>&lt; 0.001</td>
</tr>
</tbody>
</table>
## Risk of aortic dissection in syndromic vs non-syndromic patients

<table>
<thead>
<tr>
<th>Variables</th>
<th>Non-Syndromic patients (n = 84)</th>
<th>Syndromic patients (n = 16)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age at dissection (year)</td>
<td>63.2 ± 13.0</td>
<td>43.0 ± 10.7</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Number of first-degree relatives</td>
<td>7.5 ± 2.7</td>
<td>6.7 ± 1.9</td>
<td>0.288</td>
</tr>
<tr>
<td>Number of AoD events</td>
<td>1.2 ± 0.4</td>
<td>2.6 ± 0.9</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Total exposure years in adult life</td>
<td>332.8 ± 146.4</td>
<td>231.7 ± 86.7</td>
<td>0.009</td>
</tr>
<tr>
<td>Annual incidence of AoD per adult relative (%)</td>
<td>0.426 ± 0.283</td>
<td>1.282 ± 0.503</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Exposure years per relative per event</td>
<td>39.0 ± 11.1</td>
<td>14.9 ± 10.0</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Age at dissection (year)</td>
<td>63.2 ± 13.0</td>
<td>43.0 ± 10.7</td>
<td>&lt; 0.001</td>
</tr>
</tbody>
</table>
Positive FHAD dramatically increases the risk of AoD in family members
Conclusions

• A positive family history of aortic dissection confers a significantly increased risk of developing a new dissection in unaffected family members, in whom dissection occurred at younger age and after shorter exposure years.

• These findings are important to guide the strategy of screening, surveillance, and surgical management of other family members.
Clinical Implications

• Positive family history of AD may trump all other parameters as a predictor of vulnerability

• In case of positive family history of aortic dissection, early operation should be strongly considered for any first-degree relative with a documented aortic aneurysm, perhaps regardless of the aortic size

• In this era of Whole Exome Sequencing, a positive family history of aortic dissection permits identification of such vulnerable family members via shared genetic variants