Elevated Factor IX And XI Activities May Not Be a Risk Factor For Ischemic Stroke

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BACKGROUND

- Elevations of coagulation factors, such as factors IX and XI, have been established in case-control studies to contribute to venous thromboembolic (VTE) risk.
- 420 cases with DVT and 474 controls. Patients with elevated factor IX and XI levels had a mean age of 60 years, while controls had a mean age of 57 years.
- 414 cases with DVT and 474 controls. Elevated factor levels were associated with an odds ratio (OR) of 2.6 (95% CI 1.3 – 5.4), after adjustment for confounders.
- Mean levels of factor XI were equal in patients and controls.

METHODS

- Setting: Tertiary, academic hospital with comprehensive stroke service
- Study type: Prospective, case-control
- Patient Population & Study Procedures:
  - Inclusion Criteria: Adult (≥18 years) patients presenting to the ED with signs and symptoms of acute ischemic stroke resulting in activation of the Brain Attack Team from 2000-2011. Patients had to have symptom onset within 6 hours of presentation.
  - Exclusion Criteria: Patients found to have ICH. Impediments that activated the Brain Attack Team.
- Longitudinal study of 482 cases who subsequently developed VTE and 1,047 controls who remained free of thrombosis. Elevated levels of factors IX and XI were associated with an increased risk for VTE.
- Retrospective study of 78 patients with clinical history of stroke/TIA vs. 40 controls. Elevated factor XI levels were associated with an OR of 5.3 for stroke/TIA.
- Longitudinal study of 462 cases who subsequently developed VTE and 1,047 controls who remained free of thrombosis. Elevated levels of factors IX and XI were associated with an increased risk for VTE.
- Study type: Prospective, case-control

RESULTS

- No increased cases and 99 controls. See Table 1 for patient demographics and clinical information.
- Retrospective study of 78 patients with clinical history of stroke/TIA vs. 40 controls. Elevated factor XI levels were associated with an OR of 5.3 for stroke/TIA.
- Case-Control: After discharge, such study subject was adjudicated by a board-certified vascular neurologist utilizing source documents. Subjects were classified as:
  - Controls - no stroke/TIA
  - Cases - acute ischemic stroke
- Controls: acute ischemic stroke
- Excluded from analysis:
  - Patients with acute M or DTPE
  - Patients with TIA without infarct
  - Cases with stroke due to DVT or dissection
- Controls with diagnosis of "unmasking" from previous stroke
- CCS criteria: were used for stroke causative substrate classification with levels of evidence of established/potentially possible/collapsible into frequencies. More than 1 causative substrate is possible.
- Laboratory Tests: Tests performed are listed below. Tests in addition to Factors IX and XI were performed to evaluate for evidence of warfarin antagonism, liver disease, disseminated intravascular coagulation, or other abnormalities. Factor levels were determined by immunologic (nVH) or clot-based functional assays (other tests) for all patients. They were run in batches in 2011-2012.
- Factor IX and XI levels were associated with an OR of 5.3 for stroke/TIA.
- In a study from our group, we found a OR of 4.5 for TIA/CVA and an OR of 4.5 for VTE in patients with elevated factor IX activity compared to reference subjects.

CONCLUSION

Our study did not demonstrate higher mean factor IX or XI activities in subjects with ischemic stroke as compared to those with stroke mimics.

REFERENCES


Table 1: Patient Characteristics

<table>
<thead>
<tr>
<th></th>
<th>Case (n=105)</th>
<th>Control (n=99)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (mean (SD))</td>
<td>62.5 (17.8)</td>
<td>67.4 (16.7)</td>
<td>0.03</td>
</tr>
<tr>
<td>Sex (%)</td>
<td>182 (96.3)</td>
<td>97 (98.0)</td>
<td>0.32</td>
</tr>
<tr>
<td>Race (%)</td>
<td>183 (94.3)</td>
<td>96 (97.0)</td>
<td>0.32</td>
</tr>
<tr>
<td>Gender (%)</td>
<td>115 (56.4)</td>
<td>66 (62.9)</td>
<td>0.32</td>
</tr>
<tr>
<td>HTN (%)</td>
<td>46 (22.5)</td>
<td>28 (26.7)</td>
<td>0.54</td>
</tr>
<tr>
<td>DM (%)</td>
<td>49 (49.5)</td>
<td>18 (18.2)</td>
<td>0.04</td>
</tr>
<tr>
<td>Non-Hispanic (%)</td>
<td>183 (94.3)</td>
<td>96 (97.0)</td>
<td>0.09</td>
</tr>
<tr>
<td>Underdetermined cause</td>
<td>--</td>
<td>23 (23.5)</td>
<td>--</td>
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</tbody>
</table>

Table 2: Results of Coagulation Factors

<table>
<thead>
<tr>
<th></th>
<th>Case (n=105)</th>
<th>Control (n=99)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fibrinogen (%)</td>
<td>302 (63.3)</td>
<td>299 (61.3)</td>
<td>0.54</td>
</tr>
<tr>
<td>Factor IX (%)</td>
<td>137 (71.8)</td>
<td>136 (70.8)</td>
<td>0.96</td>
</tr>
<tr>
<td>Factor XI (%)</td>
<td>137 (70.8)</td>
<td>136 (70.8)</td>
<td>0.96</td>
</tr>
<tr>
<td>Mean (SD) Fibrinogen</td>
<td>317 (217)</td>
<td>321 (217)</td>
<td>0.25</td>
</tr>
<tr>
<td>Mean (SD) Factor IX</td>
<td>317 (217)</td>
<td>321 (217)</td>
<td>0.25</td>
</tr>
<tr>
<td>Mean (SD) Factor XI</td>
<td>317 (217)</td>
<td>321 (217)</td>
<td>0.25</td>
</tr>
</tbody>
</table>