SEASONAL DISTRIBUTION OF SEVERE ADAMTS13 DEFICIENT IDIOPATHIC THROMBOTIC THROMBOCYTOPENIC PURPURA

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IDIOPATHIC TTP

• Characterized by
  – Thrombocytopenia
  – Microangiopathic hemolytic anemia
  – Neurologic deficits
  – Renal injury
  – Fever

• Therapeutic plasma exchange (TPE) is first-line therapy
  – Mortality rate decreased to 10%
TTP PATHOPHYSIOLOGY

• Hyperactive interactions between unusually large vWF and platelets
  – Results in platelet thrombi within microvasculature

• Autoantibodies against enzyme ADAMTS13 associated with many cases
  – Enzyme functions as the vWF-cleaving protease
  – Antibody neutralization of enzyme results in deficiency in ADAMTS13 activity
TTP EPIDEMIOLOGY

• Risk factors include:
  – Antihypertensive medication
  – Infection
  – Diarrhea
  – Cardiovascular disease
  – Connective tissue disease
  – Prior venous thrombosis

• Specific triggers are poorly defined
SEASONS

• Environmental modulators with seasonal variation may be possible triggers
  – Allergens
  – Infectious agents
• Other autoimmune illnesses have been reported to have seasonal associations
  – Guillain-Barre Syndrome (↑ in cooler weather)
  – Rheumatoid Arthritis (↑ in Spring)
  – Systemic Lupus Erythematosus (↑ in warmer weather)
PREVIOUS SEASONAL ASSOCIATION STUDIES IN TTP

• Karimi et al, 2006

• 35 episodes of clinical TTP from 1991-2004 in Shiraz, Southern Iran
PREVIOUS SEASONAL ASSOCIATION STUDIES IN TTP

• Park *et al*, 2011, 2012
• 97 idiopathic TTP patients from 1999-2008 at the University of North Carolina at Chapel Hill
SEVERE ADAMTS13 DEFICIENT TTP PATIENTS DID NOT DEMONSTRATE A SEASONAL ASSOCIATION

<table>
<thead>
<tr>
<th></th>
<th>Severe ADAMTS13 deficiency (n = 31)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Winter</td>
<td>18.6 0.019†</td>
</tr>
<tr>
<td>Spring</td>
<td>27.8 0.309</td>
</tr>
<tr>
<td>Summer</td>
<td>36.1 N/A</td>
</tr>
<tr>
<td>Fall</td>
<td>17.5 0.012†</td>
</tr>
<tr>
<td>All seasons</td>
<td>0.012†</td>
</tr>
<tr>
<td></td>
<td>16.1 0.004†</td>
</tr>
<tr>
<td></td>
<td>25.8 0.248</td>
</tr>
<tr>
<td></td>
<td>35.5 N/A</td>
</tr>
<tr>
<td></td>
<td>22.6 0.032†</td>
</tr>
<tr>
<td></td>
<td>0.13 0.008†</td>
</tr>
</tbody>
</table>

*Severe ADAMTS13 deficiency = Activity <10%
PREVIOUS SEASONAL ASSOCIATION STUDIES IN TTP

• Hsu et al, 2011

• Initial presentations of 87 TTP patients from 2004-2010 at Washington University in St. Louis
  – 40 patients with severe ADAMTS13 deficiency
    • Defined as <5% activity and/or presence of inhibitor (iTTP)

• Majority of patients presented in warm-weather seasons

<table>
<thead>
<tr>
<th>Clinical Status</th>
<th>SPRING</th>
<th>SUMMER</th>
<th>AUTUMN</th>
<th>WINTER</th>
</tr>
</thead>
<tbody>
<tr>
<td>TTP n=87</td>
<td>10</td>
<td>31</td>
<td>23</td>
<td>23</td>
</tr>
<tr>
<td>iTTP n=40</td>
<td>5</td>
<td>15</td>
<td>14</td>
<td>6</td>
</tr>
</tbody>
</table>
PREVIOUS SEASONAL ASSOCIATION STUDIES IN TTP

• George and Vesely, 2012

• Initial presentations of 61 idiopathic TTP patients from 1996-2010 at the Oklahoma Blood Institute
  – All patients with severely deficient ADAMTS13 activity
    • Defined as <10% activity
The goal of this study was to characterize the seasonal distribution of TTP in our region.

- Multi-hospital institution
- Catchment area of ~34,000 square miles
- Covers a unique area within the northeastern, midwestern, and southern U.S.
ITXM EXPERIENCE

• Retrospective analysis of EMR
• Study period: November 2005 – October 2012
• Patients were initially identified if:
  – Consult placed to the Apheresis Service for TPE
  – ADAMTS13 activity <10%
• ADAMTS13 activity testing was performed with FRET technology in all patients
  • LIFECODES ATS-13 Activity Assay, Immucor, Inc.
237 patients with suspected clinical diagnosis of TTP

Exclusion Criteria:
- Congential TTP
- DIC
- HELLP syndrome
- Liver failure
- HIV
- Malignancy
- Malignant HTN
- Organ tx
- Pregnancy
- Active CTD
- Sepsis
- Trauma
- Drug-induced TTP

Inclusion Criteria:
- Initial Presentation since 2005
- ADAMTS13 activity <10%
- No exclusion criteria
- Diagnosis confirmed

164

73

73 Initial Presentations

16 patients with 37 Relapses

Month of Presentation and ADAMTS13 Activity Recorded
ITXM EXPERIENCE

• Both initial episodes and relapses in patients whose initial episodes occurred since 2005 were included
• Relapse = recurrence of TTP requiring re-initiation of TPE ≥ 30 days after termination of immediately previous TPE series
• Seasons defined as in previous studies
  • Spring → March-May
  • Summer → June-August
  • Autumn → September-November
  • Winter → December-February
• Goodness-of-fit chi-square analysis performed
P=0.95, All episodes
P=0.97, Initial episodes
CONCLUSIONS

• No seasonal or monthly associations identified
• Explanations for discrepant findings in other studies unknown
  – Geographic, environmental, or population differences
  – Unique infectious agents or distinct patterns of common infectious agents in different areas
  – Variability in regional patient referral biases
• Clinical vs. severely ADAMTS13 deficient TTP
  – Epidemiologically unique entities?
CONCLUSIONS

• Individual institutions should characterize their own seasonal distributions of idiopathic TTP

• This should be one part of each center’s exploration of the possible triggers of this potentially fatal illness in their respective areas
References


George JN, Vesely SK. A seasonal association of incident cases of thrombotic thrombocytopenic purpura was not observed in the Oklahoma TTP-HUS Registry. Transfusion 2012;52(7):1593-1594; author reply 1594-1595.
THANK YOU!

• QUESTIONS?