Long-Term Outcomes After Successful Treatment of TTP

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Historical Perspective

• Prior to PEX therapy nearly uniformly fatal
• Rock et al in 1991
  – PEX superior to plasma infusion
    • Mortality 10-20%
• Increasing numbers of survivors
  – Able to now evaluate for long-term issues
What Took So Long?

- Continuity of care
  - Referral back to local hematologist
  - Not followed
    - Normal platelet count, normal patient
- Longitudinal follow-up of patients
  - Emphasis of research programs
- TTP patient group meetings
  - University of Oklahoma
Neurocognitive Deficits and TTP

**Oklahoma TTP-HUS Registry**

- 24 patients with previous history of TTP
  - ADAMTS13 <10% at presentation
  - Normal physical exam
  - Normal MMSE
    - Screening for dementia

Kennedy et al. *Transfusion*, June 2009
Neurocognitive Deficits and TTP

Oklahoma TTP-HUS Registry

• Significantly worse as a group on 4/11 cognitive domains tested
  – Complex attention/concentration skills
  – Information processing speed
  – Rapid language generation
  – Rote memorization
    • 21/24 (88%) below expectations on at least 1/11 domains tested

• Not predictive: age, features of TTP, multiple episodes, interval from last episode

Kennedy et al. *Transfusion*, June 2009
Data Collection Scheme

Clinical Sites
(Columbus, USA and London, UK)

- Clinical assessment
- S100β measurement
- Neurocognitive testing
- MRI exam
- QoL assessment

- Scoring and Analysis at CogState Core Lab
- Image Analysis at Perceptive Core Lab

- OSU TTP Tissue Bank
- Scoring and Analysis at QualityMetric
CogState® Neurocognitive Test Battery

- Computerized, self-administered, rapid testing system
- Large reference dataset from normal population
- Established validity and utility for detection of disease- and drug-related neurocognitive impairment

- Detection Task – psychomotor function / speed
- Identification – attention / vigilance
- One Card Learning – visual learning & memory
- One Back Memory – working memory
- Groton Maze Learning Test – executive function
Prevalence of Neurocognitive Deficits

- 31% (9/29) unable to complete test of executive function (GMLT), no score imputed

- 62% (18/29) patients <1 SD below age-matched norm on at least 1 of the 4 other tests

- 52% (15/29) scored <2 SD below age-matched norm on at least 1 of the 4 other tests

- 45% (13/29) patients <1 SD below age-matched norm on at least 2 of the 4 other tests
Comparison of Neurocognitive Deficits in Differing Disease States

Comparison of Neurocognitive Deficits in Differing Disease States

- Depression in 35-55yrs
- 0.08% BAC in 40-50yrs
- TMA
- Dementia (AD) in 65-75yrs

DT: Detection Task
IDN: Identification Task
OBK: One Back Memory
OCL: One Card Learning
Correlations Among Measures Of CNS Injury

Neurocognitive (NC) deficits and MRI evidence of structural damage:

- 15/29 patients with NC impairment
  - 7 of these 15 also have abnormal MRI

- 9/23 patients with abnormal MRI
  - 7 of these 9 also have NC impairment

- NC testing may be more sensitive than MRI for detection of CNS injury in TMA
Long-term, sub-clinical cardiac and renal complications in patients with multiple relapses of thrombotic thrombocytopenic purpura

- At presentation
  - 17/22 (77%) with proteinuria
  - 15/22 (68%) had increased serum creatinine
- During follow-up (median 5 years)
  - Normal renal function
  - No cardiac findings
  - 2 patients with newly diagnosed HTN

Viswanathan et al. BJH, 2010
Chronic End-Organ Complications

Figure 1. Sclerotic glomeruli and atrophic tubules with petechial hemorrhage

Figure 2. Hypertrophic myocytes

Mortality and Morbidities during Long-Term Follow-Up after Recovery from Thrombotic Thrombocytopenic Purpura (TTP)

Jessica A. Reese, Zayd L. Al-Nouri, Cassandra C. Deford, Lauren M. Stewart, Deirdra R. Terrell, Sara K. Vesely, Johanna A. Kremer Hovinga, Bernhard Lämmle, James N. George
Objective

• To document the long-term outcomes of patients following recovery from TTP associated with acquired severe ADAMTS13 deficiency (<10%)
Methods: Follow-Up

• Telephone contact, 1-2 times per year

• Support group meetings, 3 times per year

• Clinic evaluation, once per year
Results

- 57 survived their initial episode:
  - median age was 39 years (range 9-71)
  - 45 (79%) were women
  - 21 (37%) were black
Hypertension

At Diagnosis

At Follow-Up

TTP Patients

Adjusted US Population

p = 0.970

p < 0.001
Diabetes

At Diagnosis

At Follow-Up

TTP Patients

Adjusted US Population

p=0.584

p=0.001
Kidney Function

- Glomerular Filtration Rate (ml/min/1.73m²)
  - TTP Patients
  - Adjusted US Population

- Albumin Creatinine Ratio (µg/mg)

<table>
<thead>
<tr>
<th>Glomerular Filtration Rate (ml/min/1.73m²)</th>
<th>&lt;30</th>
<th>30-59</th>
<th>60-89</th>
<th>≥90</th>
</tr>
</thead>
<tbody>
<tr>
<td>Percent</td>
<td>p=0.455</td>
<td></td>
<td></td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>Albumin Creatinine Ratio (µg/mg)²</th>
<th>&lt;30</th>
<th>≥30</th>
</tr>
</thead>
<tbody>
<tr>
<td>Percent</td>
<td>p=0.794</td>
<td></td>
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</table>
Probability of Survival

TTP Patients (with 95% CI)

Adjusted US Population

Time Since First Episode (Years)
## Probability of Survival

<table>
<thead>
<tr>
<th>Year(s) after initial episode</th>
<th>TTP Patients (95% CI)</th>
<th>Adjusted US Population</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>0.98 (0.87, 0.99)</td>
<td>0.997</td>
</tr>
<tr>
<td>5</td>
<td>0.90 (0.78, 0.96)</td>
<td>0.995</td>
</tr>
<tr>
<td>10</td>
<td>0.77 (0.59, 0.88)</td>
<td>0.992</td>
</tr>
<tr>
<td>15</td>
<td>0.67 (0.46, 0.82)</td>
<td>0.958</td>
</tr>
</tbody>
</table>
Attributed Causes of Death

- 1 – TTP relapse, confirmed by autopsy
- 1 – MI following recovery from TTP relapse; no TTP at autopsy
- 9 – Deaths with no evidence of TTP relapse
  - cardiovascular disease (4), ovarian cancer (1), sepsis (1), stroke (1), liver cirrhosis (1), intestinal hemorrhage (1)
Major Depression during Long-Term Follow-Up after Recovery from Thrombotic Thrombocytopenic Purpura (TTP)

Methods: Depression Measures

• Beck Depression Inventory-II (BDI-II) (2004-2011)
  – 21 question screening measure for depression within previous 2 weeks

• In-person structured psychiatric interview (2011)
  – Definitive method for diagnosis of major depressive disorder (major depression)
47 screened with BDI-II 1 – 5 times 2004 - 2011

- 15 (32%) severe depression ≥ 1 time
- 7 (15%) moderate depression ≥ 1 time
- 4 (8%) mild depression ≥ 1 time
- 21 (45%) minimal or no depression at all times
Psychiatric Interviews: 2011

15 severe BDI-II
12 survived 2011
10 (83%) psychiatric interview
9 (90%) major depression

7 moderate BDI-II
7 survived 2011
4 (57%) psychiatric interview
1 (25%) major depression
Methods: Depression Measures

• Patient Health Questionnaire-8 (PHQ-8) (2012)
  – 8 question screening measure for depression within the previous 2 weeks
  – Used by the Behavioral Risk Factor Surveillance System (BRFSS)
  – Patients were screened 6.32 years (range, 1.79-16.12 years) after their initial episode of TTP
Major Depression: PHQ-8

- Population
  - US: 3.4%
  - Oklahoma: 3.5%
  - Patients: 18.9%

95% CI (8.0, 35.2)
Conclusions

• The prevalence of major depression is significantly increased in patients during long-term follow-up after recovery from TTP

• Recognition and appropriate management of major depression are critical components of the care of these patients
The Oklahoma TTP-HUS Registry
Risk of Recurrence with a Subsequent Pregnancy

Oklahoma Registry:
– 20 women with 35 subsequent pregnancies

Systematic review of all published case reports:
– 44 articles described 49 women with 70 subsequent pregnancies

Transfusion 2004; 44:1149 (+ subsequent experience)
Recurrent TTP with a Subsequent Pregnancy

<table>
<thead>
<tr>
<th>Category</th>
<th>Oklahoma Literature</th>
</tr>
</thead>
<tbody>
<tr>
<td>Congenital</td>
<td>-</td>
</tr>
<tr>
<td>congenital</td>
<td>12/13 (92%)</td>
</tr>
<tr>
<td>Acquired</td>
<td>3/11 (27%)</td>
</tr>
<tr>
<td>idiopathic</td>
<td>11/18 (61%)</td>
</tr>
<tr>
<td>pregnancy</td>
<td>2/22 (9%)</td>
</tr>
<tr>
<td>bloody diarrhea</td>
<td>18/39 (46%)</td>
</tr>
<tr>
<td></td>
<td>0/2</td>
</tr>
</tbody>
</table>

*Transfusion 2004; 44:1149*
Pregnancy and Relapse Risk of TTP

- 5 patients with a previous history of TTP
  - 3/5 pregnancy-related (cases 1, 2, and 4)
  - 1/5 multiple previous episodes (case 3)
  - 4 required PEX based upon pretreatment ADAMTS13 activity <5%


<table>
<thead>
<tr>
<th>Case</th>
<th>Pre-pregnancy</th>
<th>10–16 weeks</th>
<th>20–26 weeks</th>
<th>Pre-delivery</th>
<th>6 weeks post partum</th>
</tr>
</thead>
<tbody>
<tr>
<td>Case1</td>
<td>&lt;5*</td>
<td>ND</td>
<td>ND</td>
<td>49*</td>
<td>ND</td>
</tr>
<tr>
<td>Case2</td>
<td>&lt;5</td>
<td>5</td>
<td>16</td>
<td>30</td>
<td>&lt;5</td>
</tr>
<tr>
<td>Case3</td>
<td>&lt;5</td>
<td>&lt;5</td>
<td>66</td>
<td>78</td>
<td>85</td>
</tr>
<tr>
<td>Case4</td>
<td>NA</td>
<td>&lt;5</td>
<td>47</td>
<td>41</td>
<td>7</td>
</tr>
<tr>
<td>Case5</td>
<td>89*</td>
<td>90*</td>
<td>78*</td>
<td>93*</td>
<td>91*</td>
</tr>
</tbody>
</table>

Samples undertaken pre-exchange in cases 1–4 undergoing regular PEX. ND: not done. NA: not applicable.

ADAMTS13 activity and the risk of thrombotic thrombocytopenic purpura relapse in pregnancy

<table>
<thead>
<tr>
<th>Patient</th>
<th>Circumstances</th>
<th>Week of gestation</th>
<th>ADAMTS13 activity (%)</th>
<th>Inhibitor level (BU)</th>
<th>Previous history of TTP</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Pregnancy-related</td>
<td>22</td>
<td>&lt;2.5%</td>
<td>1.5</td>
<td>No</td>
</tr>
<tr>
<td>2</td>
<td>Idiopathic</td>
<td>NA</td>
<td>&lt;2.5%</td>
<td>57.6</td>
<td>No</td>
</tr>
<tr>
<td>3</td>
<td>Idiopathic</td>
<td>NA</td>
<td>&lt;2.5%</td>
<td>5.2</td>
<td>No</td>
</tr>
</tbody>
</table>

Table II. ADAMTS 13 activity (inhibitor level in Bethesda units) in five pregnancies.

<table>
<thead>
<tr>
<th>Patient</th>
<th>Pregnancy</th>
<th>Pre-pregnancy (1–11 months)</th>
<th>12–20 weeks</th>
<th>20 weeks- labour</th>
<th>Postpartum (4–6 weeks)</th>
<th>TTP/week of gestation</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1</td>
<td>ND</td>
<td>ND</td>
<td>&lt;2.5% (1.5)</td>
<td>&lt;2.5% (3.2)</td>
<td>Yes/22</td>
</tr>
<tr>
<td>1</td>
<td>2</td>
<td>&lt;2.5% (0.5)</td>
<td>&lt;2.5% (0.7)</td>
<td>&lt;2.5% (19.2)</td>
<td>&lt;2.5% (0.5)</td>
<td>Yes/21</td>
</tr>
<tr>
<td>1</td>
<td>3</td>
<td>15.3% (0.5)*</td>
<td>14.8% (0.5)*</td>
<td>26% (0.5)*</td>
<td>&lt;2.5% (2)</td>
<td>No/NA</td>
</tr>
<tr>
<td>2</td>
<td>1</td>
<td>&lt;2.5% (22.4)</td>
<td>&lt;2.5% (6.4)</td>
<td>&lt;2.5% (2)</td>
<td>NA†</td>
<td>Yes/37</td>
</tr>
<tr>
<td>3</td>
<td>1</td>
<td>61.2% (0.5)</td>
<td>100% (0.5)</td>
<td>91.7% (0.5)</td>
<td>ND</td>
<td>No/NA</td>
</tr>
</tbody>
</table>
Conclusions

• Significant increase in our knowledge of the long-term complications from a previous diagnosis of TTP
  – Greater number survivors
  – Patient support group

• Neurocognitive, vascular, and psychiatric complications are more common than recognized previously

• Increased awareness may lead to efforts to decrease the morbidity and mortality related to these chronic complications